NHS Evidence - oral health
Byte sized oral health information

ORAL CANCER
ANNUAL EVIDENCE UPDATE
November 2009
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>2</td>
</tr>
<tr>
<td>Commentary</td>
<td>3</td>
</tr>
<tr>
<td>Topics</td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td>12</td>
</tr>
<tr>
<td>Prevention</td>
<td>14</td>
</tr>
<tr>
<td>Diagnosis and referral</td>
<td>15</td>
</tr>
<tr>
<td>Prognosis (no new reviews/guidelines identified)</td>
<td>17</td>
</tr>
<tr>
<td>Treatment and Management</td>
<td>19</td>
</tr>
<tr>
<td>Oral Care for Cancer Patients</td>
<td></td>
</tr>
<tr>
<td>Patient Information</td>
<td>21</td>
</tr>
<tr>
<td>Methodology</td>
<td>22</td>
</tr>
</tbody>
</table>
Introduction

Professor Barbara Chadwick
Clinical Lead for NHS Evidence – oral health

Welcome to the 2009 Oral Cancer Annual Evidence Update which, once again is published during Mouth Cancer Awareness Week (15-21 November 2009). The Update provides a summary of the best available clinical information published over the past year.

We are delighted to present a commentary on the evidence written by Dr David Conway, Clinical Senior Lecturer at the Dental School and Honorary Consultant in Dental Public Health at NHS National Services Scotland (NSS). His systematic review on social inequalities and oral cancer risk was one of the most interesting identified in our last update.

NHS Evidence - oral health has identified and critically appraised new systematic reviews in oral cancer and cancer of the head and neck. Broader cancer reviews have also been included where they include relevant studies. In addition, the collection has worked with the National Library of Guidelines to identify the latest guidelines meeting their inclusion criteria. The Update has been divided into the following categories:

- Risk factors
- Prevention
- Diagnosis and referral
- Prognosis (note – no new reviews or guidelines identified)
- Treatment and management
- Oral Care for Cancer Patients

In each category, new evidence is presented first, followed by the results of our two previous updates.

Finally, I would like to express my thanks to those involved in developing this Annual Evidence Update. First to those who have volunteered their time: Dr Conway for his highly insightful commentary, and the members of the Editorial Board who provided a clinical perspective on the critical appraisals. I would also like to thank Fiona Morgan and Ruth Turley, Information Specialists on the NHS Evidence – oral health team who have been responsible for searching and critically appraising the literature and who have done much of the work to pull the update together.

Barbara Chadwick is Professor of Paediatric Dentistry and Student Affairs Tutor at Cardiff University School of Dentistry
As we enter Mouth Cancer Awareness Week [1] it is a good opportunity to reflect on the body of literature published in the past 12 months. This research has aimed to further our understanding of the aetiology of oral cancer and to inform the development of evidence based practice to better treat and manage patients with the disease.

The need for reflection seems to be greater than ever – with the spotlight on oral cancer as it regularly hits the headlines in the UK. “Alarming rise in oral cancer rates among forty somethings” [2] and “Drink blamed for oral cancer rise” [3] were typical stories which focused on the increasing rates of the disease in young people, and on the role of excessive alcohol consumption in oral cancer risk. Their source was the Cancer Research UK publication of epidemiological statistics for oral cancer incidence [4].

However, behind these eye-catching headlines, a detailed interrogation of the data reveal that the facts remain: oral cancer is a disease primarily of older adults (the median age is 65), is more common among men (males : females ratio is 2 : 1 – albeit this ratio has been converging) and is increasing among those living in our most deprived communities [5].

In the UK there were 5,325 new cases and 1,841 deaths in 2007 from oral cancer in the UK [3]. Globally head and neck cancers are among the most common in the world accounting for over 550,000 new cases and over 300,000 deaths per year [6] – with the greatest burden falling upon low- and medium-income countries [6]. Survival for patients with head and neck cancer is poor and there has been limited improvement in the last three decades [7].

This commentary sets out to identify and review all systematic reviews published in the past year which included oral cancer as a focus, to critically appraise them, and to interpret the evidence. The broad areas of oral cancer research included here fall into the following categories and will be considered in turn:

- Risk factors
- Prevention
- Diagnosis and referral
- Treatment and management
- Clinical guidelines

I must acknowledge the support I received from the NHS Evidence - oral health team, who identified and critically appraised all the reviews included in this commentary.

Newly published evidence in 2009

There were 15 systematic reviews and 2 clinical guidelines related to oral cancer published in the year November 2008 to October 2009 – they are summarised in Table 1 and Table 2 respectively.
### Table 1: Systematic reviews in oral cancer in 2009

<table>
<thead>
<tr>
<th>Paper</th>
<th>Research Area</th>
<th>Study Type</th>
<th>Quality Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al, 2009 [8]</td>
<td>Risk associated with smokeless tobacco</td>
<td>Meta-analysis of 98 studies (8 cohort, 90 case control)</td>
<td>Weak data, methodological flaws in review and authors have significant competing interests</td>
</tr>
<tr>
<td>Smith et al, 2009 [12]</td>
<td>Risk biomarkers in dysplasia</td>
<td>Systematic review and meta-analysis of 13 observational studies</td>
<td>Well conducted review but included studies were of poor quality</td>
</tr>
<tr>
<td>Zhou et al, 2009 [13]</td>
<td>Risk genetic risk factor</td>
<td>Systematic review and meta-analysis of 8 case control studies (1326 cases and 3,130 controls)</td>
<td>Poor quality studies and review had methodological flaws</td>
</tr>
<tr>
<td>Zhuo et al, 2009 [14]</td>
<td>Risk genetic risk factor</td>
<td>Systematic review and meta-analysis of 27 case control studies</td>
<td>Review has methodological flaws; lack of information on potential confounders</td>
</tr>
<tr>
<td>Kim 2009 [16]</td>
<td>Prevention garlic</td>
<td>Narrative systematic review, includes 1 case control study relevant to oral cancer</td>
<td>Poorly conducted review with weak data</td>
</tr>
<tr>
<td>Boehm et al, 2009 [17]</td>
<td>Prevention green tea</td>
<td>Systematic review includes 1 prospective cohort study relevant to oral cancer</td>
<td>Cochrane review conducted using a high quality methodology. Limited data of medium quality</td>
</tr>
<tr>
<td>Gómez et al, 2009 [19]</td>
<td>Diagnosis and referral diagnostic delay</td>
<td>Systematic review and meta-analysis of 9 retrospective cross-sectional studies</td>
<td>Significant flaws in review methodology and limited quality data</td>
</tr>
<tr>
<td>Goy et al, 2009 [20]</td>
<td>Diagnosis and referral diagnostic delay</td>
<td>Narrative systematic review of 27 studies; study type not defined</td>
<td>Review of limited methodological quality. Significant clinical heterogeneity</td>
</tr>
<tr>
<td>Huang et al, 2009 [21]</td>
<td>Diagnosis and referral tumour thickness and cervical lymph involvement</td>
<td>Systematic review of 16 studies; study type unclear. Pooled data for total of 1136 patients</td>
<td>Review has some methodological flaws. Studies had limited sample size</td>
</tr>
<tr>
<td>Bohlius et al, 2009 [22]</td>
<td>Treatment and management erythropoietin</td>
<td>Narrative systematic review. 3 RCTs included patients with head and neck cancer only</td>
<td>Cochrane review using appropriate methodology. Sequence generation unclear in all three studies, allocation concealment unclear in one study</td>
</tr>
<tr>
<td>Kassab et al, 2009 [23]</td>
<td>Treatment and management homeopathic medicines for adverse effects</td>
<td>Narrative systematic review. 2 RCTs included patients with head and neck cancer</td>
<td>Cochrane review conducted using a high quality methodology. Sequence generation and allocation concealment unclear in studies</td>
</tr>
<tr>
<td>Kedge 2009 [24]</td>
<td>Treatment and management moist desquamation in radiotherapy</td>
<td>Narrative systematic review of 9 RCTs and 1 CCT</td>
<td>Well conducted review, limited by having one author. Overall study quality poor</td>
</tr>
<tr>
<td>Lambin et al, 2009 [25]</td>
<td>Treatment and management erythropoietin</td>
<td>Systematic review and meta-analysis of 5 RCTs of patients with head and neck cancer</td>
<td>Cochrane review using appropriate methodology. Only one study showed no risk of bias</td>
</tr>
<tr>
<td>LeBon et al, 2009 [26]</td>
<td>Treatment and management topical opioids in palliative care</td>
<td>Systematic review of 6 RCTs and 13 case reports</td>
<td>Review has some methodological flaws. Studies of low to medium quality</td>
</tr>
</tbody>
</table>
Table 2: Clinical guidelines in oral cancer in 2009

<table>
<thead>
<tr>
<th>NICE Guideline [28]</th>
<th>Cetuximab for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck</th>
<th>Clinical Guideline</th>
<th>Appropriate high quality methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHS Clinical Knowledge Summary [29]</td>
<td>Head/neck cancer - suspected</td>
<td>Evidence based practice review</td>
<td>Appropriate high quality methodology</td>
</tr>
</tbody>
</table>

Risk associated with smokeless tobacco

Lee et al’s [8] systematic review and meta-analysis investigating the relationship between smokeless tobacco and all cancer is a follow-up from their 2007 review which focussed entirely on oral cancer [9]. Their new study found an additional three studies on the risk in oral cancer. They found similar results in both reviews with a significant increased risk for oral cancer associated for past smokeless tobacco use in the USA but not for Scandinavian snuff.

The authors declare competing interests in the form of consultancy work for “a number of tobacco, pharmaceutical and chemical companies”. Without doubting the scientific ethics of the individual authors – it is disappointing that doubts around the motivation and purpose of this research inevitably appear at the back of one’s mind while reading this review. There is a well documented significant debate on whether tobacco funded research is ethical and should be published in the scientific literature at all [10, 11]. However, on the plus side for this review, the authors’ conflicts of interest are up front, declared and not hidden.

**Key message:** There is a lower risk of oral cancer associated with smokeless compared to smoking tobacco. As this risk still remains and is significant, it would be difficult to justify advising use of smokeless tobacco as a strategy in smoking cessation.

Biomarkers in dysplasia of the oral cavity

Smith et al [12] undertook a well-conducted systematic review into biomarkers for oral cancer. There were methodological limitations in their review primarily associated with limitations in the underlying studies – including wide study heterogeneity, small sample sizes and design of the studies included in the review. Therefore, the results need to be interpreted with caution. The main findings were the identification of a range of pathological and genetic biomarkers in oral dysplasia that are associated with progression to oral cancer.

**Key message:** There is potential to identify biomarkers to help predict oral cancer progression risk in patients with oral dysplastic lesions. This in turn could change clinical practice in terms of targeting of treatment and follow-up. More and better research is required to hone these findings.

Genetic risk factors of oral cancer

Zhou et al [13] identified the Arg194Trp polymorphism in the X-ray repair cross-complementing group 1 gene as a potential risk factor of oral cancer in a meta-analysis of 8 case-control studies. The search and quality assessment within the review was limited. The risk of oral cancer among Asians associated with this gene was quantified as a 35% increased risk. This gene has been described as potentially modifying the effects of smoking and betel quid chewing.

The same group also undertook a further meta-analysis investigating CYP1A1 and GSTM1 polymorphisms - Zhou et al [14]. Both genotypes were not significant in Asian or white populations

**Key message:** Identification of genetic markers in the future could inform risk assessment and treatment planning. We remain a while away from definitive applications in practice.
Further research on risk factors for oral cancer

Large international consortia are increasingly coming together to undertake pooled analysis. In relation to epidemiological research - the International Head and Neck Cancer Epidemiology (INHANCE) consortium, established in 2004 to contribute elucidating the aetiology of head and neck cancer by providing opportunities for pooled analyses of individual patient data on head and neck cancer on a very large scale (with 33 studies pooling data on nearly 25,000 cases and over 33,000 controls) [15]. This is the way forward with regard to elucidating better understanding of risk factors for oral cancer.

Prevention of oral cancer

Kim conducted a very interesting review into the association with garlic intake and reduced cancer risk [16]. In relation to cancer in general there was limited evidence to support the role of garlic in cancer prevention. But one case-control study reported a near 40% reduced cancer risk associated with high consumption of garlic.

Green tea was the focus of a high quality Cochrane review by Boehm and colleagues [17]. They found insufficient evidence to give any firm recommendations regarding green tea for cancer risk or indeed prevention in general or oral cancer in particular.

In terms of diet and oral cancer risk, with the exception of the well known risk associated with alcohol consumption, there is only reasonable evidence (from systematic reviews) to support the role of fresh fruit and vegetables in reducing oral cancer risk [18].

Key message: Prevention strategies in terms of behavioural risk factors need to continue to focus on reducing smoking and alcohol consumption, and increasing fruit and vegetable consumption.

[Those who enjoy green tea and garlic should continue to do so!]

Diagnosis and referral

Diagnosis delay was investigated in a meta-analysis by Gómez et al [19]. Viewing the results with caution, primarily due to the limitations of the original research included in the review – delay in diagnosis was broadly associated with more advanced stage disease compared to patients with no delay. More research is clearly required in this area, including prospective studies with strict methodology. Both patient and service side factors need to be considered – often delay is put down to patients’ not seeking care, when there may be barriers to this care and delays associated with identification and referral that need to be better understood and ultimately improved.

Goy et al undertook a similar systematic review for head and neck cancer – including oral cancer [20]. While the review was well conducted, it suffered from the very mixed nature (high heterogeneity) of the studies included. This review found no evidence to support the relationship between patient delay and tumour stage at diagnosis. This is counterintuitive, but perhaps suggests that it doesn’t matter how late the diagnosis is – getting any stage of diagnosis of oral cancer is too late. Further work is also required to investigate diagnosis delay related to staging and to prognosis.

Key message: Services need to be oriented to and focus on early diagnosis, but further research is required to understand how to improve this.

Huang et al in their meta-analysis confirmed a strong association between tumour thickness and cervical lymph-node involvement [21]. While the meta-analysis was not of the highest quality, the strength of association would seem to over-ride this concern.

Key message: Tumour thickness is a valid predictor in planning neck treatment. The optimal cut-off point for tumour thickness is 4mm - with oral tumours thicker than this requiring a prophylactic neck dissection.

Reviews on treatment
Bohlius et al [22] undertook a Cochrane review including analysis of individual patient data to investigate erythropoietin or darbepoetin treatment in cancer patients. The review followed robust Cochrane methodology and included only three head and neck cancer trials (out of 53 cancer trials in the whole review). Erythropoietin or darbepoetin treatment worsened survival overall (there was no specific oral or head and neck analysis). For those patients undergoing chemotherapy, the worsening was less pronounced.

Lambin and colleagues [25] undertook a Cochrane review specifically into the use of erythropoietin as an adjuvant treatment with (chemo) radiation therapy for head and neck cancer. Interestingly, by contrast to Bohlius, they identified five trials, they did however agree that erythropoietin with radiotherapy had worse outcomes than radiotherapy alone.

**Key message:** There is not enough evidence to support the use of erythropoietin treatment in head and neck cancer patients undergoing radiotherapy and limited evidence even as an adjuvant to chemotherapy.

Kassab et al [23] undertook their Cochrane review into the controversial area of homeopathic medicines and their potential role in limiting adverse effects from cancer treatments. Robust methodology found some preliminary data in support of the efficacy of topical calendula for prophylaxis of acute dermatitis during radiotherapy and Traumeel S mouthwash in the treatment of chemotherapy-induced stomatitis.

The area of homeopathic medicines is controversial and it can only become more credible if further and more robust randomised control trials are undertaken. Thus far, there have been limited randomised control trials in this area.

**Key message:** More research is required into homeopathic medicines in managing adverse effects in cancer treatments.

There was a systematic review investigating the effectiveness and acceptability of interventions for moist desquamation in radiotherapy patients by Kedge [24]. Moist desquamation is a nasty side-effect of radiotherapy where the skin thins and weeps as it loses its epithelial integrity. In a very well conducted systematic review, including one head and neck cancer trial amongst the 10 included, a mixed picture of evidence was found regarding the use of hydrogels and hydrocolloid dressings – but they sometimes improved patient comfort (although not other aspects of the condition – such as duration). There was no evidence to support other interventions for moist desquamation.

**Key message:** Hydrogels and hydrocolloid dressings can improve patient comfort in those with moist desquamation following radiotherapy.

LeBon and co-workers in a thorough systematic review found some evidence to support the use of topical opioids in the palliative care for cancer patients [26]. The review included only one head and neck trial (out of the 6 RCTs and 13 case reports identified in the review). However there is limited evidence to transfer this to clinical practice in terms of ideal opioid, starting dose, interval of administration, methods of titration, or carrier, nor which wounds are suitable for this treatment.

**Key message:** There is not enough evidence to support the use of topical opioids in head and neck cancer patients.

Stableforth et al [27] undertook a systematic review into the role of immunonutrition in patients undergoing surgery for head and neck cancer. The review had limited methodology providing evidence mostly from small trials with incomplete reporting. The pooled estimates showed a reduction in length of hospital stay with perioperative immunonutrition – but the mechanism was unclear.

**Key message:** Further research in the form of adequately powered trials need to be undertaken to substantiate the benefits of immunotherapy in patients undergoing surgery for head and neck cancer (although the evidence is beginning to look promising).

**Guidelines published in 2009**

In the past year, two relevant clinical guidelines have also been published. There was a NICE Guideline on Cetuximab for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck [28]. NICE concluded that cetuximab, given in combination with platinum-based chemotherapy for the treatment of recurrent and/or metastatic
squamous cell carcinoma of the head and neck, could not be recommended as a cost-effective use of NHS resources. The NICE Committee noted that some people may be currently receiving cetuximab in combination with platinum-based chemotherapy for this indication and recommended that these people should have the option to continue treatment until they and their clinician consider it appropriate to stop.

NICE decisions on the cost-effectiveness of medication often receive adverse publicity. In this current economic climate, decisions around cost-effectiveness are ever more important as the health service has tighter financial constraints. But, to some degree, it was always thus – there is always a finite level of resource and decisions to fund one treatment (particularly costly and not fully clinically proven treatments) have an opportunity cost and impact on funding other areas of the health care.

A Clinical Knowledge Summary on what health care practitioners should do if head and neck cancer is suspected was also published in this past year [29]. All of the general recommendations were considered at the lowest level (D) evidence – which indicates that they are based primarily from evidence from expert committee reports, opinions and/or clinical experience of respected authorities. This highlights the need for more research into head and neck/oral cancer.

**Key message:** A patient who presents with symptoms suggestive of head and neck or thyroid cancer should be referred to an appropriate specialist or the neck lump clinic, depending on local arrangements

Any patient with persistent symptoms or signs related to the oral cavity in whom a definitive diagnosis of a benign lesion cannot be made, should be referred or followed up until the symptoms and signs disappear. If the symptoms and signs have not disappeared after six weeks, an urgent referral should be made.

Primary health professionals should advise all patients, including those with dentures, to have regular dental checkups.

Finally, in relation to the evidence for the primary treatment and management of oral cancer, the Cochrane Systematic Reviews on Oral Cancer (CSROC) group [30] are working on systematically reviewing the evidence in relation to oral cancer treatment and management. While the review into surgical treatment has already been published [31], the work continues in relation to chemotherapy, radiotherapy, and immunotherapy/biotherapy [32].

**References**


32. Cochrane Library Database of Published Protocols http://www.ohg.cochrane.org/reviews.html#protocols [accessed November, 2009].
Risk Factors

Systematic Reviews


**Authors’ conclusions**: Meta-analyses based on smoking-adjusted estimates for a relatively wide range of cancers show no indication of an increased risk of cancer for snuff, as used in Scandinavia. The overall data for oropharyngeal cancer shows a significant increase in risk associated with smokeless tobacco (ST) use, but this is not evident for estimates adjusted for smoking and alcohol, or for studies published since 1990. Any effect of ST may relate mainly to products used in the past in the USA. A weak but significant association with prostate cancer, based on limited data from US studies, requires more confirmatory evidence. Reports of significant associations with pancreatic and esophageal cancer in an earlier review are not confirmed, and reasons for this will be discussed in a later publication. Risk from ST products as used in North America and Europe is clearly very much less than that from smoking, and is not evident at all in Scandinavia.

**Quality**: The results of this review should be viewed with caution. As the authors highlight, “the available data relating to smokeless tobacco use have a number of weaknesses, including inadequate control for smoking in many, and limited data for never smokers. In addition, they declare competing interests in the form of consultancy work for “a number of tobacco, pharmaceutical and chemical companies”. The review was funded by the European Smokeless Tobacco Council and previous related work by Philip Morris International.

In addition, it is possible that potentially relevant studies were missed as only one database (Medline) was searched using restrictive search terms supplemented by reference list checking. Included studies were all from Scandinavia or the USA, (studies in Asian and African populations were excluded). It is unclear whether non-English language studies were included.

No information is provided on the methods used to select, quality assess and data extract included studies and the introduction of error and bias cannot be excluded. The authors discuss a range of methodological issues and highlight weaknesses.


**Authors’ conclusions**: Many methodological limitations have been identified by this review and we recommend the results are interpreted with caution. Research into this field should concentrate on longitudinal design, with pooling of data from multiple centres to achieve larger cohorts. We recommend standardisation of definitions to allow appropriate comparisons to be made.

**Quality**: Overall a well-conducted systematic review. As the authors indicate, their conclusions should be interpreted with caution, given the methodological limitations of included studies.

The authors made a reasonable attempt to identify available literature, searching a wide range of electronic databases (Cochrane Library, Embase, Medline, AMED, CINAHL and Kings Fund), albeit with limited search terms. They also conducted an internet search, checked reference lists and contacted experts. However, as they concede, restricting inclusion to published English language studies may have introduced bias.
Appropriate methods were used to minimise error and bias in study selection, quality assessment and data extraction. The quality of included studies was assessed using the Newcastle-Ottowa Scale – a validated checklist for observational studies. The authors highlight the limited quality of included studies – generally small scale, single centre, retrospective observational studies.


Authors’ conclusions: We suggest that the Arg194Trp polymorphism in the XRCC1 gene may be a biomarker of oral cancer susceptibility among Asian population.

Quality: As the authors indicate in the full text, the review is limited by the quality of the included studies. It is likely that potentially relevant studies were missed. Although there were no language restrictions, only one database (PubMed) was searched using limited search terms, supplemented by reference list checking. Whilst unpublished studies were not sought, a check did not reveal publication bias. The review was limited to case control studies, although no reason is given for this. Selection criteria for other reviews identified in this area also include cohort studies.

Appropriate methods were used to minimise error and bias in study selection and data extraction. The authors do not report conducting quality assessment of the included studies although they identify several methodological flaws that may have introduced bias, including the use of hospital-based controls, a lack of information on potential confounders and small sample sizes.


Authors’ conclusions: The data suggest that variant genotypes of CYP1A1 might not be risk factors for oral cancer, whereas GSTM1 null genotype significantly increases susceptibility to oral cancer in Asians but not Caucasians.

Quality: The results of this review should be viewed with caution. It is likely that potentially relevant studies were missed. The search was restricted to three general medical databases (Medline, Embase and CNKI) using limited search terms. Searching genetics databases, supplemented by reference list checking, hand searching key journals and consulting experts may have identified additional research.

It is unclear how study selection was conducted. However, an appropriate process was used to minimise error and bias in data extraction. No formal quality assessment was undertaken, but the authors do discuss some quality issues including sample size and the risk of various biases. Whilst the lack of information on socio-economic status in some studies is highlighted, sensitivity analyses do not appear to have been conducted for this or for other key confounders such as tobacco and alcohol usage. The only sub-group analyses reported were those for Asians and Caucasians.
Prevention

Systematic Reviews


Authors’ conclusions: There was no credible evidence to support a relation between garlic intake and a reduced risk of gastric, breast, lung, or endometrial cancer. Very limited evidence supported a relation between garlic consumption and reduced risk of colon, prostate, esophageal, larynx, oral, ovarian, or renal cell cancers.

Quality: The results of this review should be viewed with caution. It is likely that potentially relevant studies were missed as the search was restricted to published papers in English and Korean identified from two electronic databases (Medline and Embase) using limited search terms. The search was supplemented only by references obtained from two colorectal cancer systematic reviews. Additional reference list checking, consulting experts, searching grey literature sources and including studies in other languages may have identified additional studies. It is notable that the authors do not reference an earlier high quality AHRQ systematic review on this topic: Mulrow et al 2000. Garlic: effects on cardiovascular risks and disease, protective effects against cancer, and clinical adverse effects.


Authors’ conclusions: There is insufficient and conflicting evidence to give any firm recommendations regarding green tea consumption for cancer prevention. The results of this review, including its trends of associations, need to be interpreted with caution and their generalisability is questionable, as the majority of included studies were carried out in Asia (n = 47) where the tea drinking culture is pronounced. Desirable green tea intake is 3 to 5 cups per day (up to 1200 ml/day), providing a minimum of 250 mg/day catechins. If not exceeding the daily recommended allowance, those who enjoy a cup of green tea should continue its consumption. Drinking green tea appears to be safe at moderate, regular and habitual use.

Quality: A Cochrane review conducted using a high quality methodology.

Guidelines

No new guidelines were identified.
Systematic Reviews


Authors’ conclusions: The probability for patients with delayed diagnosis to present an advanced-stage tumour at diagnosis was significantly higher than that of patients with no delay in diagnosis. However, new prospective studies with strict methodology are needed to shed more light on this association.

Quality: The results of this review should be viewed with some caution, given the limited quality of the evidence identified. As the authors state, there is a need for well-conducted prospective studies. In addition, it should be noted that, despite high levels of heterogeneity overall, discussion focuses on the results of fixed effects analyses, rather than the more appropriate random effects analyses. The former are statistically significant, where the latter are generally not significant.

The authors searched several databases (Medline, Embase and ISI) without language restrictions, supplemented by reference list checking. Whilst only published studies were included, a test for publication bias was negative.

Appropriate methods were used to minimise the risk of introducing error and bias in study selection, quality assessment and data extraction. The authors used elements of the MOOSE reporting checklist to consider quality; specifying three criteria: follow-up period; measurement of potential confounders; results stratified by anatomical location.


Authors’ conclusions: Possible explanations for the lack of an observed relationship between patient delay and stage include: inaccurate measurement of delay, lack of sensitivity of disease stage to delay-related disease progression, and variation in tumor aggressiveness, which could lead to variation in symptom progression rates. Better evidence is needed about the relationship between diagnostic delay and disease progression and/or disease outcomes. If demonstrated and validated, such associations would provide a much stronger argument than description of delay alone for education programs around symptom recognition and for more active screening of high-risk individuals.

Quality: This review is limited by considerable clinical heterogeneity between the included studies; notably in the number of sites included, the variety of types of delay and the ways in which delay was measured.

The authors searched three databases (Medline, Embase and Biosis) and supplementing their search with reference list checking. However, it is likely that studies were missed and bias introduced as the search terms used were extremely limited and the search was restricted to published studies in the English language. No information is provided on the processes used to select and data extract included papers. Whilst no formal quality assessment process is described, several elements were identified in the inclusion criteria including study design and sample size.

**Authors’ conclusions:** Considerable variation on the strength of association between tumor thickness and cervical lymph-node involvement is noted. This is attributed to study heterogeneity, imprecise definitions of tumor thickness and limited sample sizes. An association between tumor thickness (TT) and cervical lymph-node involvement is confirmed in this study. The optimal cutoff point for TT is 4 mm. For oral cavity tumors thicker than 4 mm, prophylactic neck management is generally recommended. Standardization of the measuring method of TT is required for using TT as valid predictor in planning neck treatment. A less invasive method of assessment is needed if this parameter is to be incorporated into clinical TNM staging system.

**Quality:** The authors searched two databases (Medline and Embase) supplemented by reference list checking. However, the limited search terms and the restriction to published studies in the English language, makes it likely that potentially relevant studies were missed and bias introduced.

Appropriate procedures were used to minimise error and bias in study selection, data extraction and quality assessment. However, whilst the authors state that they assessed methodological quality they do not provide information on the outcome of this assessment.

**Guidelines**

*Head/neck cancer - suspected* (Clinical Knowledge Summary)
Treatment and Management

**Systematic Reviews**


**Authors' conclusions:** ESA treatment in cancer patients increased on study mortality and worsened overall survival. For patients undergoing chemotherapy the increase was less pronounced, but an adverse effect could not be excluded.


**Authors' conclusions:** This review found preliminary data in support of the efficacy of topical calendula for prophylaxis of acute dermatitis during radiotherapy and Traumeel S mouthwash in the treatment of chemotherapy-induced stomatitis. These trials need replicating. There is no convincing evidence for the efficacy of homeopathic medicines for other adverse effects of cancer treatments. Further research is required.


**Authors' conclusions:** Despite being recommended by many guidelines (College of Radiographers Summary of Intervention for Acute Radiotherapy Induced Skin Reactions in Cancer Patients (London, 2001); NHS Quality Improvement Scotland Best Practice Statement: Skincare of Patients Receiving Radiotherapy (Edinburgh, 2004)); there is mixed evidence concerning the use of hydrogels and hydrocolloid dressings. However, improved patient comfort was sometimes seen, which is arguably equally important. There was limited evidence to support other interventions. Further research is urgently needed.

**Quality:** Overall a well-conducted systematic review, however, as the author states, the generalisability of most included studies is limited by small samples, strict selection criteria, single centre locations and restricted patient groups.

An extensive electronic search of 24 sources was conducted for published and unpublished literature in all languages. The search was supplemented by hand searching, reference list checking and contacting experts and manufacturers.

The review was conducted by a single author and consequently it is possible that bias and error were introduced in selecting, quality assessing and data extracting studies. The CASP checklist was used to quality assess included studies. Study quality was mixed.


**Authors' conclusions:** There are strong suggestions that RT plus EPO has a negative influence on outcome as opposed to RT alone. However, the target haemoglobin concentration, which was higher than recommended in four of
the five included RCTs, may have had a significant role. Nevertheless, based on these findings EPO should not be administered as an addition to RT outside the experimental setting for patients with head and neck cancer.


**Authors’ conclusions:** This review concludes that there is support for the use of topical opioids, but does not permit us to make clear recommendations for clinical practice in terms of the ideal opioid, the starting dose, interval of administration, methods of titration, or carrier, nor are we able to identify which wounds are most suitable for this treatment. Despite clear clinical benefits described in small RCTs, there is a deficiency of higher-quality evidence on the role of topical opioids, and more robust primary studies are required to inform practice recommendations. N-of-1 trials should be encouraged for specific clinical circumstances.

**Quality:** The authors searched a wide range of databases (Medline, Embase, CINAHL, CancerLit, controlledtrials.com and Evidence-based Medicine Reviews) supplemented by reference list checking and hand searching. However the search terms used were limited and may not have identified all relevant papers. Whilst grey literature sources were searched, inclusion was limited to published studies in English and German languages which may have introduced bias.

No information is provided on the process used to select studies for inclusion, but data extraction was conducted by two reviewers. The quality of the six RCTs was assessed using the Jadad scale and was found to be limited in three studies (lack of blinding and small sample sizes were mentioned). Only limited information is provided on the quality and the results of included studies.


**Authors’ conclusions:** There is a discrepancy between the use of dietary interventions and the strength of evidence for their benefit. Whilst perioperative immunonutrition is associated with reduced length of hospital stay; the mechanism is unclear as other outcomes were not improved. Trials were small with incomplete reporting of outcomes. An adequately powered trial is required to substantiate benefit.

**Quality:** The authors made a reasonable attempt to identify the available literature, searching several databases, albeit with limited search terms, supplemented by reference list checking and contacting manufacturers to identify unpublished studies. It is not clear whether there were any language restrictions.

It is unclear how study selection and quality assessment was conducted. However, an appropriate process was used to minimise error and bias in data extraction. The authors assessed key quality elements: allocation concealment, use of ITT analysis and blinding of participants and assessors. They also comment on small sample sizes with consequent inadequate powering of studies.

**Guidelines**

Cetuximab for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck (NICE 2009).
Oral Care for Cancer Patients

Systematic reviews


**Author's conclusions:** Despite being recommended by many guidelines (College of Radiographers Summary of Intervention for Acute Radiotherapy Induced Skin Reactions in Cancer Patients (London, 2001); NHS Quality Improvement Scotland Best Practice Statement: Skincare of Patients Receiving Radiotherapy (Edinburgh, 2004)); there is mixed evidence concerning the use of hydrogels and hydrocolloid dressings. However, improved patient comfort was sometimes seen, which is arguably equally important. There was limited evidence to support other interventions. Further research is urgently needed.

**Quality:** Overall a well-conducted systematic review, however, as the author states, the generalisability of most included studies is limited by small samples, strict selection criteria, single centre locations and restricted patient groups.

An extensive electronic search of 24 sources was conducted for published and unpublished literature in all languages. The search was supplemented by hand searching, reference list checking and contacting experts and manufacturers. The review was conducted by a single author and consequently it is possible that bias and error were introduced in selecting, quality assessing and data extracting studies. The CASP checklist was used to quality assess included studies. Study quality was mixed.


**Authors’ conclusions:** This review concludes that there is support for the use of topical opioids, but does not permit us to make clear recommendations for clinical practice in terms of the ideal opioid, the starting dose, interval of administration, methods of titration, or carrier, nor are we able to identify which wounds are most suitable for this treatment. Despite clear clinical benefits described in small RCTs, there is a deficiency of higher-quality evidence on the role of topical opioids, and more robust primary studies are required to inform practice recommendations. N-of-1 trials should be encouraged for specific clinical circumstances.

**Quality:** The authors searched a wide range of databases (Medline, Embase, CINAHL, CancerLit, controlledtrials.com and Evidence-based Medicine Reviews) supplemented by reference list checking and hand searching. However the search terms used were limited and may not have identified all relevant papers. Whilst grey literature sources were searched, inclusion was limited to published studies in English and German languages which may have introduced bias.

No information is provided on the process used to select studies for inclusion, but data extraction was conducted by two reviewers. The quality of the six RCTs was assessed using the Jadad scale and was found to be limited in three studies (lack of blinding and small sample sizes were mentioned). Only limited information is provided on the quality and the results of included studies.
Leukoplakia. NHS Choices.

Mouth Cancer. NHS Choices
Methodology

Search strategy

The following search strategy was developed in Medline and adapted to the remaining databases.

1. mouth neoplasms.ti,ab. or exp Mouth Neoplasms/
2. "head and neck neoplasms"/
3. exp mouth neoplasms/
4. ((cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or metatasta$) adj5 (oral$ or intra-oral$ or gingiva$ or oropharyn$ or mouth$ or tongue$ or cheek or cheeks or gum or gums or palatal or palate or intraoral or (head adj neck))).ti,ab.

5. or/1-4
6. meta-analysis.pt,sh.
7. (meta-anal: or metaanal:).tw.
8. (quantitativ: review or quantitativ: overview:).tw.
9. (systematic: review: or systematic: overview:).tw.
10. (methodologic: review: or methodologic: overview:).tw.
11. (integrative research review: or research integration:).tw.
12. quantitativ: synthes:.tw.
13. or/6-12
14. (medline or mediars).tw,sh. or embase.tw.
15. (scisearch or psychinfo or psycinfo).tw.
16. (psychlit or psyclit).tw.
17. (hand search: or manual search:).tw.
18. (electronic database: or bibliographic database:).tw.
19. (pooling or pooled analys: or mantel haenszel).tw.
20. (peto or der simonian or dersimonian or fixed effect:).tw.
21. or/14-20
22. review.pt,sh. or review:.tw. or overview:.tw.
23. 21 and 22
24. 13 or 23
25. 5 and 24
26. limit 25 to (english language and yr="2008 - 2009")

Databases and other sources

We searched the following electronic sources for systematic reviews, meta-analyses and guidelines published in English between November 2008 and October 2009.

Amed
ASSIA
CINAHL
Embase
Medline
Medline-in-Process
PsycINFO
Cochrane Database of Systematic Reviews
DARE
NHS Choices, the British Dental Health Foundation and cancer charity websites were searched for patient information.

We hand searched or scanned the electronic tables of contents of eight oral health journals:
- British Dental Journal
- International Journal of Oral & Maxillofacial Implants
- International Journal of Oral & Maxillofacial Surgery
- Journal of Dental Research
- Journal of Dentistry
- Journal of Oral & Maxillofacial Surgery
- Journal of the American Dental Association
- Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics

**Inclusion Criteria**

To be included in the collection, a systematic review had to meet the following criteria:
- Search strategy includes at least one electronic database
- Inclusion and exclusion criteria detailed
- Included studies have been quality assessed
- Results of the included studies are reported

**Results**

The search strategy identified 370 potentially relevant systematic reviews. After scanning the titles and abstracts, 242 duplicate references and clearly irrelevant records were removed. 128 papers were reviewed in full-text, of which 15 systematic reviews met the collection’s inclusion criteria. Two new guidelines were also identified.

**Critical appraisal**

Journal-published systematic reviews that had not been appraised for the Database of Abstracts of Reviews of Effects (DARE) were critically appraised by Information Specialists from the NHS Evidence – oral health using internationally recognised methods and a critical summary was produced. The critical appraisal, summary and paper of each included review has been checked by a clinician for accuracy and contextual issues.