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Review

Biomarkers in dysplasia of the oral cavity: A systematic review

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SUMMARY

Oral dysplasia is a potentially precancerous lesion diagnosed histologically. While the risk of progression is associated with histological grade, it is currently impossible to predict accurately which lesions will progress. More accurate markers predicting progression to cancer would enable the targeting of these lesions for more aggressive treatment and closer follow-up. We have performed a systematic review with pooling of data to assess the evidence for the use of biomarkers in predicting transformation of oral dysplasia into cancer. We systematically searched the Cochrane library, MEDLINE, EMBASE, AMED, Cinahl and the Kings Fund electronic databases using the terms: oral dysplasia, leukoplakia, erythroplakia, biomarkers and genetic markers. The following *a priori* selection criteria were used: longitudinal cohort or case-controlled studies of oral dysplasia that progressed to cancer. Cross-sectional studies and studies reporting only on leukoplakia were excluded. Data were extracted by two reviewers. Quality assessment was carried out using validated tools. We assessed the relative risk of progression form oral dysplasia to cancer and pooled data where possible. 2550 studies were identified, from which 288 were scrutinised in greater detail. Of these, 247 were excluded, mainly due to cross-sectional design. Of the 41 studies containing follow-up data, 28 were excluded, most commonly due to data only being available for lesions once they had progressed to cancer. A lack of clear histological definition of oral lesions was also a common finding. Data were extracted from 13 longitudinal studies. The evidence consists mainly of small, single centre, retrospective studies. In oral dysplasia, loss of heterozygosity (LOH), particularly at the 3p ± 9p loci, increases the risk of progression to cancer (RR 17.60 (2.77, 108.37) $p < 0.001$), as does survivin (RR 30 (4.25, 197.73), $p \leqslant 0.001$), matrix metalloproteinase (MMP 9), (RR 19.00 (1.56, 209.38) $p = 0.02$) and DNA content (RR 12.00 (1.17, 82.10) $p = 0.03$). Other markers identified by this review including p53, p73, MMP 1 and 2 and cathepsin L mRNA, did not predict progression. LOH, survivin, MMP 9 and DNA content are potential markers for increased risk of progression from oral dysplasia to cancer. Many methodological limitations have been identified by this review, however, and we recommend these 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.

Background

Oral dysplasia is a relatively common precursor of oral cancer. Progression to cancer varies widely ranging from 6% to 36%.[1] Histological grade is currently the best predictor of progression to cancer and provides the basis on which clinical decisions are made. The grade of dysplasia is determined by the degree of cellular abnormality above the epithelial basement membrane as originally defined by the World Health Organisation (WHO).[2]

The most recent WHO publication indicates that there is no clear consensus on the most clinically appropriate grading system for oral dysplasia.[3] Many factors play a part in this. Accuracy of grading is dependant on the quality of tissue and the site at which a biopsy is taken. Dysplasia grading is also subjective, with inter and intra-rater variability.[4,5] Furthermore, some lower grades of dysplasia progress to cancer whilst other, higher grades, remain static or even regress, irrespective of environmental factors.[6] A better system for the prediction of cancer progression is therefore needed.

Objectives

This systematic review examines the current evidence for the effectiveness of biomarkers and genetic abnormalities in predicting progression to cancer in patients with oral dysplasia.

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Methods

Search strategy

Our search strategy was developed in accordance with guidelines outlined in the Cochrane handbook for systematic reviews.[7] We searched and identified articles using the Cochrane library (1995-November 2007), MEDLINE (1950-November 2007), EMBASE (1974-November 2007), AMED (1985-November 2007), Cinahl (1982-November 2007) and the Kings Fund (1979-November 2007). The search was widened to include the Internet and handsearched reference lists of identified articles. We consulted experts within the field for further identification of relevant material. No language restrictions were imposed on the initial search.

In order to maximise identification of relevant articles we used the key phrase 'oral dysplasia' as our initial search term. In a second search, the keywords 'oral dysplasia,' 'leukoplakia' and 'erythroplakia' were individually cross referenced with the terms 'biomarkers,' 'genetic markers' and 'molecular markers.'

Selection criteria

Article titles and abstracts were reviewed and irrelevant papers were excluded (Fig. 1). If the abstract was deemed relevant then the full paper was reviewed for suitability by two researchers (JS, TR). If there was disagreement on the inclusion of a study then a third reviewer (HM) was consulted.

We limited selection to human studies of oral dysplasia defined on standardised histological assessment as outlined by the WHO.[2] Studies including oral lesions defined clinically, such as leukoplakia and erythroplakia, were excluded unless data on dysplasia were reported separately and could be extracted from published tables. We included all longitudinal studies that presented data for progressing and non-progressing oral dysplasias. These included case-control and cohort studies as well as consecutive case series. Both prospective and retrospective studies were included. Progressing lesions were defined as those dysplasias that developed cancer at the same site as the initial biopsy when followed over time. Non-progressing lesions were those matched comparisons followed for a similar or longer period that did not progress to cancer.

Cross-sectional studies of biomarkers in oral dysplasia were included in descriptive analysis only and excluded from prognostic analyses. Studies including cases where cancer developed at other sites were excluded. Studies including cases with a previous history of oral cancer or previous treatment for oral cancer were also excluded.

Data extraction and analysis

Once the final selection of articles for inclusion had been agreed, two researchers (JS, TR) independently extracted data using a standardised data table (Table 1) and a third researcher (HM) checked the data. Two researchers independently assessed the quality of identified studies using the validated, Newcastle Ottawa Scale (NOS), for quality assessment in observational studies.[8] This tool was used to assess the selection method, comparability of cases and exposure. It generates a rating out of nine.

Data on the same marker were grouped. Dichotomous variables were analysed in two by two tables. SAS version 9.1 was used to calculate relative risk, p values and to assess heterogeneity.

Outcome measures

We examined the risk of progression from oral dysplasia to cancer in the presence or absence of identified markers.

Results

Description of studies

Search results

The selection and exclusion process based on the literature search is shown in Fig. 1. Our search strategy identified 2550 citations that were reviewed for suitability for inclusion. 288 citations were identified as warranting further examination. The abstracts

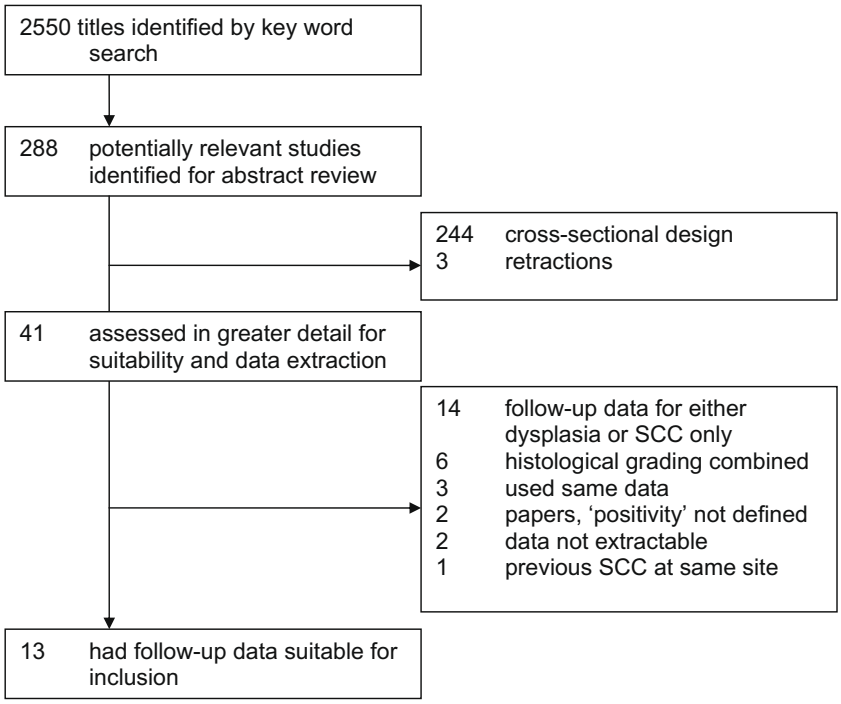

Figure 1 Flow diagram for study selection.