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Review

Diagnostic capability of salivary biomarkers in the assessment of head and neck cancer: A systematic review and meta-analysis

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SUMMARY

The purpose of this systematic review and meta-analysis was to evaluate the diagnostic value of salivary biological markers in the diagnosis of head and neck carcinoma. Studies were gathered by searching Cochrane, EMBASE, LILACS, MEDLINE, and PubMed. The references were also crosschecked and a partial grey literature search was undertaken using Google Scholar. The methodology of selected studies was evaluated using the 14-item Quality Assessment Tool for Diagnostic Accuracy Studies. After a two-step selection process, 15 articles were identified and subjected to qualitative and quantitative analyses. The studies were homogeneous, and all had high methodological quality. Combined biomarkers demonstrated better accuracy with higher sensitivity and specificity than those tested individually. Furthermore, the salivary biomarkers reviewed predicted the early stages of head and neck carcinoma better than the advanced stages. A restricted set of five single biomarkers (interleukin-8, choline, pipecolinic acid, L-phenylalanine, and S-carboxymethyl-L-cysteine) as well as combined biomarkers demonstrated excellent diagnostic test accuracy. The present systematic review confirms the potential value of a selected set of salivary biomarkers as diagnostic tools for head and neck carcinoma.

Introduction

Cancer of the head and neck is a relatively uncommon human cancer. The term "head and neck cancer" covers a large number of neoplasms with a diverse natural history arising in one anatomic region. Head and neck cancer includes tumors of the mucosa of the upper aerodigestive tract including the oral cavity, pharynx, larynx, and sinuses [1]. Among all subtypes, carcinoma of the mouth and pharynx together rank as the sixth most common neoplasm. The tongue is the most common head and neck cancer site among European and US populations, contributing to 40–50% of oral squamous cell cancers (OSCC). The prevalence of head and neck cancer varies widely and there is wide geo-demographic variation (approximately 20-fold) in the incidence of head and neck squamous cell carcinoma (HNSCC). The risk of developing oral cancer increases with age and the majority of cases occur in people aged 50 or over [2]. The most important etiological factors are cigarette smoking and alcohol use [3], although high-risk human papillomavirus (HPV), particularly HPV-16, has been recognized as an independent factor for a subset of HNSCC, and there is a strong association between HPV infection and development of tonsil carcinoma [4]. Despite all of the diagnostic and therapeutic advances, the 5-year survival rate of patients with HNSCC remains relatively unfavorable, around 50% [1].

The gold standard for HNSCC diagnosis is a biopsy followed by a histopathological analysis, although this method has several important limitations. The scalpel biopsy for diagnosis is invasive and associated with increased patient morbidity. It is reserved for evaluating highly suspicious lesions and not for the majority of oral lesions that are not clinically suspicious. Furthermore, scalpel biopsy is subject to significant inter- and intra-observer variability in the histologic diagnosis of dysplasia. The relative complexity, low access, and high costs of the gold standard approach employed for diagnosing the vast majority of head and neck cancer has urged the field to search for alternative diagnostic methods [5].

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At present, several therapeutic approaches are used in the management of cancer, but they are typically aggressive and associated with numerous side effects that significantly reduce the patient's quality of life [1]. The main treatments for HNSCC are surgery, radiotherapy, chemotherapy, or a combination of two or more of these techniques [6]. The search for new HNSCC therapies should consider both the ability of patients to tolerate the treatment's side effects and the toxicity associated with that treatment [7]. To reduce the side effects and toxicity caused by these conventional treatments, researchers have put forth great effort to develop effective and less invasive diagnostic methods capable of identifying the early stages of HNSCC. At present, the available methods for early diagnosis include brush biopsy, toluidine blue staining, auto-fluorescence, spectroscopy, and genomic, transcriptomic, proteomic and metabolomic strategies for the detection of saliva biomarkers [5,8–10].

The study and use of saliva-based diagnostics has increased exponentially during the past 10 years. Saliva-based clinical testing is a promising noninvasive method for the diagnosis of several diseases [11,12]. The "omic" approaches have allowed for the discovery and validation of several salivary biomarkers to detect HNSCC [10,13]. Despite promising emerging results, additional research in this area is necessary before saliva as a diagnostic fluid can be effectively implemented in clinical practice.

An ideal biomarker should have some critical characteristics such as disease specificity, mandatory presence in all affected patients (i.e., high sensitivity and specificity), reversibility following proper treatment, and detectability before patients develop obvious clinical manifestations of disease. Furthermore, ideal biomarkers should reflect not only the severity of the disease, but also provide information about the cumulative history of the disease, while enabling a cut-off value with minimal overlap between normal and disease states [14] .

Evidence suggests that salivary biomarkers are a viable diagnostic option. However, it is necessary to determine which of the numerous reported biomarkers exhibit acceptable diagnostic test accuracy (DTA). Thus, the purpose of this systematic review and meta-analysis was to summarize the results of all published studies on salivary biological biomarkers and evaluate the diagnostic value of those biomarkers for head and neck carcinoma.

Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA Checklist [15] .

Protocol and registration

This systematic review protocol was registered at the international prospective register of systematic reviews (PROSPERO) as CRD42015016390.

Study design

A systematic review of human studies was undertaken to evaluate the diagnostic value of salivary biological markers in the diagnosis of HNSCC.

Eligibility criteria

Inclusion criteria

Articles that focused on salivary biological markers in the diagnosis of HNSCC located in the lip and/or oral cavity, pharynx, larynx, nasal cavity, or paranasal sinuses were selected [16]. Studies in which salivary biological media were used as a potential diagnostic media and/or to monitor adults patients with HNSCC compared with non-HNSCC controls were also considered.

Exclusion criteria

The following studies were excluded: (1) those that used different biological media such as blood or body fluids instead of saliva as potential media diagnostics and/or to monitor adults patients with HNSCC; (2) those that were not research articles, including reviews, letters, personal opinions, book chapters, and conference abstracts; and (3) those that reported associations between saliva and cancer in experimental studies (in vitro or in vivo animal studies).

Information sources and search strategy

Detailed individual search strategies for each of the following bibliographic databases were developed: Cochrane, EMBASE, LILACS, MEDLINE, and PubMed (Appendix 1). A partial grey literature search was performed using Google Scholar. The search included all articles published on or before November 13, 2014, across all databases, with no time or language restrictions. The references were managed manually and duplicate hits were removed. The references cited in the selected articles were also checked for any incremental references that were inadvertently omitted during the electronic database searches.

Study selection

The study selection was completed in two phases. In phase one, two authors (ENSG and ACA) independently reviewed the titles and abstracts of all the references. These authors selected articles that appeared to meet the inclusion criteria based on their titles and abstracts. A third author (HC) was involved when disagreements emerged between the two initial evaluators. Any studies that did not fulfill the inclusion criteria were discarded. In phase two, full articles were evaluated to determine those studies that reported sensitivity and specificity or in which the data presented enabled these diagnostic assessments to be extrapolated. Studies that included insufficient information for meta-analysis were excluded. ENSG and ACA independently participated in phase two. Reference lists for all included articles were critically assessed by ENSG. The articles that were selected from the reference lists were read by ENSG and ACA. Any disagreement in either phase was resolved by discussion and mutual agreement among the three reviewers (ENSG, ACA, and HC). Final selection was always based on the full-text of the publication.

Data collection process

ENSG and HC collected the required information from the selected articles. ACA crosschecked the collected information and confirmed its accuracy. Again, any disagreement in either phase was resolved by discussion and mutual agreement among ENSG, ACA, and HC. A fourth reviewer (GDL) was involved as required, to enable formulation of the final decision.

Data items

For all of the included studies, the following information was recorded: year of publication, author(s), country, sample size (cases of HNSCC and non-HNSCC controls), patient age, study methods, type of biomarkers, class, and main conclusions. If the required data were not complete, attempts were made to contact the authors to retrieve the missing information.