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Diagnostic accuracy of serum biomarkers for head and neck cancer: A systematic review and meta-analysis

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ABSTRACT

Serum biomarkers could be helpful to characterize head and neck squamous cell carcinoma (HNSCC). Thus, the purpose of this systematic review and meta-analysis was to determine the diagnostic capability of serum biomarkers in the assessment of HNSCC patients. Studies were gathered by searching LILACS, PubMed, Science Direct, Scopus and Web of Science up to April 10th, 2015. Studies that focused on serum biomarkers in the diagnosis of HNSCC compared with controls were considered. Sixty-five studies were identified, and the sample size included 9098 subjects. Combined biomarkers demonstrated improved

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accuracy than those tested individually. Therefore, 12.8% of single and 34.3% of combined indicated that serum biomarkers discriminate patients with HNSCC from controls. The combined biomarkers with better diagnostic capability included Epidermal growth factor receptor (EGFR) + Cyclin D1 and squamous cell cancer-associated antigen (SCCA) + EGFR + Cyclin D1. $Beta_2$-microglobin may also be a promising single biomarker for future studies. Serum biomarkers can be potentially useful in the diagnosis of HNSCC. However, further research is required to validate these biomarkers.

1. Introduction

Biomarkers have emerged as critically important tools to detect diseases in their various clinical stages by increasing the accuracy to precisely characterize the disease in a diagnostic or prognostic level (Yotsukura and Mamitsuka, 2015). Serum biomarkers are more appealing due to the simplicity of obtaining blood samples. There are several serum biomarkers that are routinely used in clinical oncology, such as prostate specific antigen (PSA) for prostate cancer and cancer antigen (CA)-125 for ovarian cancer. However, their applications have significant limitations because of their relatively low specificity (Heidenreich et al., 2008). Protein biomarker discovery for early detection of head and neck squamous cell carcinoma (HNSCC) is a critically unmet need in the efforts to improve patient outcomes. Therefore, mass spectrometry-based proteomics has emerged as a promising tool for identification of biomarkers in different cancer types (Marimuthu et al., 2013).

Most HNSCC develop in the upper aero-digestive epithelium after exposure to carcinogens such as tobacco and alcohol (Shah and Gil, 2009; Warnakulasuriya, 2009a, 2009b). Human papillomavirus has also been strongly implicated as a causative agent in a subset of these cancers (Thavaraj et al., 2011). Disappointingly, survival has not markedly improved in recent decades because patients still frequently develop local and regional recurrences, distant metastases and second primary tumors (Leemans et al., 2011). At present, several therapeutic approaches are used in the management of HNSCC, but they are typically aggressive and associated with numerous side effects that significantly hamper patient quality of life (Shah and Gil, 2009). The main treatments for HNSCC are surgery, radiotherapy, chemotherapy, or a combination of two or more of these techniques (Pedruzzi et al., 2008). 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 (Cabrera et al., 2013). To reduce the side effects and toxicity caused by these conventional treatments, researchers have invested great efforts to develop effective and less invasive diagnostic methods capable of identifying HNSCC at early stages.

To date, 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 serum biomarkers (Mehrotra and Gupta, 2011; Zhang et al., 2013; Patel and Ahmed, 2014; Cheng et al., 2014). Biopsy, followed by a histopathological analysis, is considered the gold standard for HNSCC diagnosis, although this method has several important limitations. The relative complexity and low access 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 (Mehrotra and Gupta, 2011).

Discovery of diagnostic markers has increased exponentially during the past 20 years. Serum-based clinical testing is a relatively noninvasive method for the diagnosis of several diseases (Lutzky et al., 2008; Baum et al., 2011; Streckfus and Bigler, 2002). Despite promising emerging results, additional research in this area is necessary before serum as a diagnostic fluid can be effectively implemented in clinical practice. Although there is a large number of old and recent studies reporting on the associations between serum biomarkers and HNSCC, a systematic review and meta-analysis is necessary to determine which of the numerous collections of reported biomarkers actually exhibits acceptable diagnostic test accuracy (DTA). Thus, the purpose of this systematic review and meta-analysis was to answer a focused question, namely: "Do serum (blood) biomarkers have the capability to accurately identify HNSCC patients from non-HNSCC controls?"

2. Methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA Checklist (Moher et al., 2010). The review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD 42015020817.

2.1. Study design

A systematic review of human studies was undertaken to summarize the results of all published studies on serum biological markers and evaluate the diagnostic value of those biomarkers for HNSCC.

2.1.1. Inclusion criteria

Articles that focused on serum biological markers in the diagnosis of HNSCC located in the lip and/or oral cavity, pharynx and larynx, were selected (Sobin et al., 2009). Studies in which serum 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. Only studies in Latin (Roman) alphabet were considered.

2.1.1. Exclusion criteria

The following exclusion criteria were applied: (1) Different biological media such as saliva or other body fluids instead of serum were used as a potential media diagnostics and/or monitoring adults patients with head and neck cancer; (2) Nasopharyngeal carcinoma (EBV viral) due to its unique differences in etiology, epidemiology and therapeutic options (Chan and Felip, 2009); (3) Biomarkers for prognosis and/or follow-up; (4) Reviews, letters, personal opinions, book chapters, and conference abstracts; (5) Association between serum and cancer in experimental studies (*in vitro* or *in vivo* animal studies); (6) Studies that did not report sensitivity and specificity; 7) Insufficient information for meta-analysis or results not individualized for HNSCC; (8) Language restrictions; (9) Full paper copy is not available.

2.2. Information sources and search strategy

Detailed individual search strategies for each of the following bibliographic databases were developed: LILACS, PubMed, Science Direct, Scopus and Web of Science (Supplementary Table S1 in the