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Salivary biomarkers in the diagnosis of breast cancer: A review

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ABSTRACT

Salivary biomarkers could be helpful to characterize breast cancer. Therefore, this review was performed to evaluate the capability of salivary biological markers in the diagnosis and monitoring of breast cancer. Studies were eligible for inclusion if they assessed the potential diagnostic value or other discriminatory properties of biological markers in saliva of patients with breast cancer. The search was performed in six electronic databases (Cochrane, LILACS, PubMed, Science Direct, Scopus, Web of Science). In addition the biomarkers were classified according to their potential clinical application. We identified 567 pertinent studies, of which 13 met the inclusion criteria. Combined biomarker approaches demonstrated better ability to predict breast cancer patients than individual biomarkers. As single biomarker, namely proline, reported great capacity

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in both early and late stage breast cancer diagnosis. Taurine showed interesting capability to identify early breast cancer individuals. Furthermore, valine also demonstrated excellent diagnostic test accuracy for advanced stages of breast cancer. Only seven studies reported sensitivity and specificity (Zhang et al., 2010; Streckfus et al., 2000a; Brooks et al., 2008; Cheng et al., 2015; Bigler et al., 2002; Zhong et al., 2016; Streckfus, 2009), which varied considerably from 50% to 100%, and from 51% to 97%, respectively. In general, salivary biomarkers identified advanced stages of breast cancer better than early stages. There is currently limited evidence to confirm the putative implementation of salivary biomarkers as diagnostic tools for breast cancer. However, current review provides new research directions.

1. Introduction

Globally, breast cancer is the most frequently diagnosed malignity, corresponding to over a million cases each year (Globocan, 2012). It is also the leading cause of cancer-related deaths in women worldwide (Siegel et al., 2013). The incidence rates are highest in North America, Australia/New Zealand, and in Western and Northern Europe, and lowest in Asia and sub-Saharan Africa (Jemal et al., 2011). These geodemographic differences are likely related to societal changes as a result of industrialization (e.g., changes in fat consumption, body weight, early menarche and reproductive patterns such as fewer pregnancies and later age at first birth) (Ahlgren et al., 2004). In the United States, breast carcinoma accounts for at least 230,000 cases each year and is responsible for over 40,000 deaths (Siegel et al., 2013). Its mortality rate has been decreasing since the 1970s (Kohler et al., 2015). This decrease in mortality is likely due, at least in part, to improved breast cancer screening and adjuvant therapy (Narod et al., 2015).

Early detection of breast cancer offers the promise of easier treatment (smaller surgeries, less radiation or chemotherapy) and improved survival. Conventional screening (physical examination and mammography) has a less-than-desirable sensitivity and specificity (Berg et al., 2004). At present, screening mammography is considered the gold standard for detection of breast cancer; however, the sensitivity of this test is between 54% and 77% depending on the type of mammographic procedure (Berg et al., 2004). Thus, women who undergo a putatively negative annual mammography may still present with breast cancer. False-positive rates in breast cancer screening are also a notable limitation, as high callback rates and dispensable biopsies, increase cost, radiation dose, and patient apprehension (Drukteinis et al., 2013). A relevant obstacle towards early recognition of breast carcinoma is the development of methods that conveniently and accurately identify potentially affected individuals (Etzioni et al., 2003). The improvement in early detection of breast cancer is essential for successful patient management (Arellano et al., 2009). To confirm the diagnosis of breast cancer, breast biopsies as core biopsy or mammotomy are followed by a histopathological and immunohistochemistry analysis, although limitations of these methods have already been reported (Zhang et al., 2013). The biopsy for diagnosis is invasive and associated in some cases with patient morbidity. The relative complexity, low access, and high costs of the gold standard approach employed for diagnosing the vast majority of breast cancer cases has urged the field to search for alternative diagnostic methods to improve early detection (Zhang et al., 2013).

Technological advancements have benefited biomarker research to the point where saliva is now recognized as an excellent diagnostic vehicle that can be collected simply and noninvasively. Increasing interest has developed in the last decade on the use of saliva as an adjunct test that enhances conventional medical assessment approaches to serious systemic diseases (Streckfus and Bigler, 2005; Streckfus and Bigler, 2002). A sensitive assay that readily and accurately identifies biomarkers using non-invasively collected clinical specimens would be optimal for breast cancer detection and screening (Zhang et al., 2010). As a diagnostic medium, saliva has several biochemical advantages when compared with blood. The collection of saliva is safe (i.e., no needle punctures), noninvasive and relatively simple, and may be collected repeatedly without discomfort to the patient (Mandel, 1990). In this regard, analyses of salivary biomarkers offer additional advantages, since they are a filtrated fraction of the blood, thereby reflecting the physiological conditions of the body, such that salivary samples could be used to monitor clinical status and predict systemic diseases (Sugimoto et al., 2010; Lawrence, 2002; Bigler et al., 2009). Saliva-based diagnostics, particularly those based on metabolomic technologies, are emerging and offer a promising clinical strategy, characterizing the association between salivary analyses and a particular disease (Sugimoto et al., 2010).

The capability of salivary biomarkers in the assessment of other cancers has been studied, e.g. head and neck cancer (Guerra et al., 2015), but the cumulative experience in the context of breast cancer remains unclear. In this context, the aim of this review was to critically evaluate the potential of salivary biomarkers in breast cancer diagnosis, and to provide new directions for future studies.

2. Methods

2.1. Protocol and registration

The protocol was registered at the international prospective register of systematic reviews (PROSPERO) under number CRD42015024085.

2.2. Study design

A review evaluating the capability of salivary biomarkers for assessment of breast cancer diagnosis and to monitor treatment of patients with advanced disease was undertaken.

Articles that focused on salivary biological markers in the diagnosis of breast cancer were included. Studies in which salivary biological media were used as a potential diagnostic media and/or to monitor adults patients with breast cancer compared with non-breast cancer controls were also considered.

Studies were excluded for the following reasons: (1) those that were not primary research articles, including reviews, letters, personal opinions, book chapters, and conference abstracts; (2) studies that did not evaluate biomarkers for diagnosis in breast cancer; (3) those that used different biological media such as blood or body fluids instead of saliva as potential media diagnostics and/or to monitor adult patients with breast cancer.

2.3. Study selection

Studies to be considered for inclusion were identified using search strategies for each of the following electronic databases: Cochrane, LILACS, PubMed, Science Direct, Scopus, Web of Science