Screening of Oral Cancer Using Plasma Biomarkers

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ABSTRACT

Aim of the work: there are many types of biomarkers (DNA biomarkers, RNA biomarkers and protein biomarkers). They have a pivotal role in early detecting of oral cancer. In this review, we aimed to summarize the potent plasma biomarkers which have been reported to have pivotal role in the detection and diagnostic different types of oral cancer. **Methods**: an electronic search in MEDLINE was conducted through PubMed using this search strategy (Plasma biomarker or plasma indictors) and (Oral cancer or oral tumor or oral squamous cell carcinoma). The search resulted in 158 eligible study and finally 10 potential articles were included in this systematic review. **Results**: in general, 9 articles used oral squamous cell carcinoma (OSCC) while, only one study used gingival squamous cell carcinoma as a type of oral cancer in order to evaluate the potential of biomarker to detect oral cancer. In eight articles microRNAs were predominantly used as potent biomarkers, different types of microRNAs were used. Plasma hsa-miR-542-3p recorded potential performance as biomarker in diagnosis of OSCC with AUC 0.82. Down regulation of hsa-miR-542-3p were correlated with increasing of surviving expression in OSCC. **Conclusion**: we can conclude that plasma microRNAs biomarkers occupied wide scope of the included studies in this review and could be serve as potent and sensitive biomarkers (especially plasma miR-125b expression and combination of miR-196a and miR-196b) for prognostic and diagnostic different types of oral cancer.
Keywords: oral cancer, biomarkers, plasma, screening, DNA, RNA, protein.

INTRODUCTION

Oral cancer is classified as one of the most prevalent cancer around world [1,2]. The wide spread for this malignant disease is associated with some of unhealthy habits as smoking and alcohol addicting, in addition to molecular mutations which are considered as carcinogenesis agent [3]. Early detection for oral cancer may help to reduce patient morbidity and mortality. This mainly depends on the early and accurate diagnosis [4]. There are some substances defined as biomarkers produced by tumor or by normal tissue which can be used as specific markers for detecting cancer or monitoring the progression of therapeutic response. Biomarkers may be a single molecular or a series of molecules which could be detected in a variety of body fluids as plasma and salivary [5, 6]. There are many types of biomarkers (DNA biomarkers, RNA biomarkers and protein biomarkers) which have a pivotal role in early detecting of oral cancer [7]. Cytokines (Pro-inflammatory, anti-inflammatory and chemokines) may release from the tumor and surrounding lymphocytes and could be used as biomarkers in early detecting of oral cancer. **Tachibana *et al.***[8] revealed that in their study on plasma miRNAs biomarkers in patients with gingival squamous cell carcinoma (GSCC) plasma miR-223 level in gingival squamous cell carcinoma differed significantly from that in the controls, therefore they reported that miR-223 could serve as diagnostic biomarker and act as a tumor suppressor inhibited cell proliferation and induced apoptosis. **Gu *et al.***[9] reported that plasma miR-125b was as promising plasma biomarker for detecting oral squamous cell carcinoma(OSCC). It had strong ability to differentiate OSCC from healthy controls. Significantly increasing of plasma miR-125b expression was detected in patients with OSCC compared to healthy controls. Other studies revealed that the combined determination of plasma miRNAs could be considered as potential diagnostic biomarkers for OSCC. **Lu *et al.***[10] showed that, the combined determination of miR-196a and miR-196b levels recorded excellent accuracy, sensitivity and specificity in the prediction of oral cancer. Furthermore, Su, *et al.*[11] suggested that plasma TIMP3 was a potential biomarker for predicting the tumor stage and T status in patients with OSCC.

In this review we aimed to summarize the potent plasma biomarkers which have been reported to have pivotal role in the detection and diagnostic different types of oral cancer.

METHODS

An electronic search in MEDLINE was conducted through PubMed using this search strategy "plasma biomarker" or plasma indictors and "oral cancer" or "oral tumor" or "oral squamous cell carcinoma". The search resulted in 158 eligible study, 135 articles were irrelevant when their title and abstract were screened, 127 irrelevant articles, five reviews and three
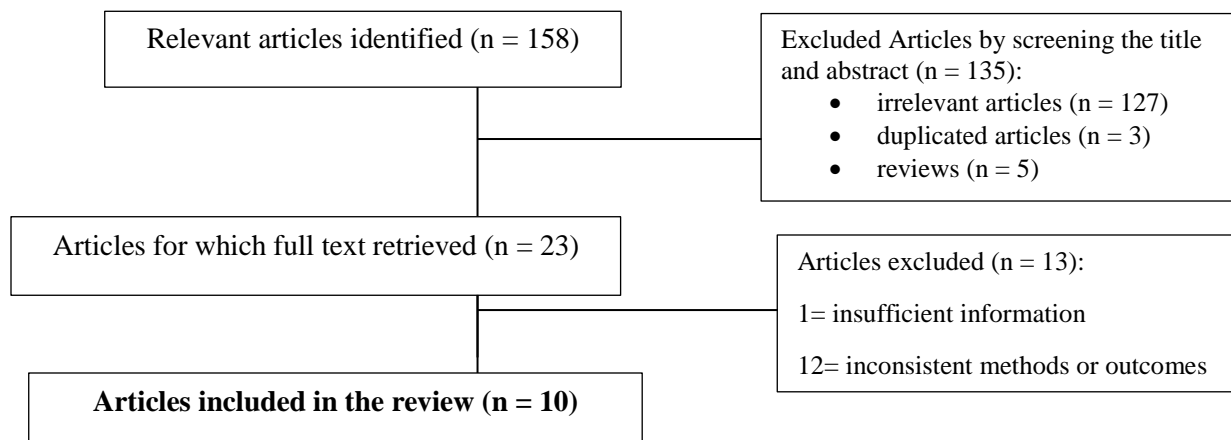
duplicated articles. The full texts were retrieved for 23 studies, after that 13 articles were excluded, one of them had insufficient information and 12 articles were inconsistent outcomes. Ten potential articles [8-17] were included in this systematic review to summarize the accuracy, sensitivity or specificity of plasma biomarkers for detecting different type of oral cancer **(Table 1).** The protocol of this review was registered and approved in Prospero database of York University.

RESULTS

A total of 158 articles were collected after searching from PubMed and after exclusion of irrelevant, duplicated and studies with inconsistent outcomes, 10 studies were included (**Figure 1).** In general nine articles [9-17] used oral squamous cell carcinoma (OSCC), while only one study [8] used gingival squamous cell carcinoma (GSCC) as a type of oral cancer in order to evaluate the potential of biomarker to detect oral cancer. In eight articles [8-10, 13-17] microRNAs were predominantly used as potent biomarkers, different types of microRNAs were used. Plasma hsa-miR-542-3p recorded potential performance as biomarker in diagnosis OSCC with AUC 0.82. Down regulation of hsa-miR-542-3p were correlated with increasing of surviving expression in OSCC [13] . **Tachibana et al.**[8] introduced circulating miR-223 as a novel diagnostic biomarker and as therapeutically target for gingival squamous cell carcinoma with AUC 0.703, sensitivity 67.7% and specificity 61.3%. Highest accuracy (0.966) and specificity (93.5%) were estimated for plasma miR-125b among all plasma biomarkers in the included studies. Plasma miR-125b recorded strong

ability to differentiate OSCC from healthy the controls [9].**Lu et al.**[10] showed that the combined determination of miR-196a and miR-196b levels recorded excellent accuracy (0.950) and specificity (85%) with the highest sensitivity (91%) in the prediction of potential malignancy, and can be used a panel plasma biomarkers in early detection of oral cancer. High expression of miR-196a in cancer tissue with miR-196a2 gene polymorphism were reported as prognostic predictors for OSCC with AUC 0.75[14]. Plasma miR-181a and miR-181b has been exploited as putative biomarker for detecting OSCC, they have been used to differentiate oral malignant from non-malignant status with AUC 0.84 for miR-181a, AUC 0.74 for miR-181b and AUC 0.89 for combined of miR-181a and miR-181b [15]. Plasma miR-31 was validated to use as a good biomarker for diagnostic OSCC. Increasing levels of miR-31 in plasma was used as a potential marker for oral cancer with AUC 0.72 [16].

Lin et al.[17] found that the plasma levels of miR-24 in OSCC patients were significantly higher than that in control; miR-24 was used as biomarker for detection patients with OSCC with AUC 0.73. Other types of investigated plasma biomarkers were tissue inhibitor metallo proteinase-3 (TIMP3) and carbonic anhydrase IX (CAIX). TIMP3 had ability to predict the tumor stage and tumor status in OSCC patients with AUC 0.835, sensitivity 69.6% and specificity 84.4% [11], whereas CAIX was suggested as a non- invasive biomarker to monitor progression in OSCC patient. The significant higher levels of CAIX were determined in OSCC patient when compared to that in the control with AUC 0.74, sensitivity 83.6% and specificity 54.9% [12].

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┌─────────────────────────────────┐          ┌──────────────────────────────────────┐
│ Relevant articles identified     │          │ Excluded Articles by screening the    │
│ (n = 158)                        │──────────│ title and abstract (n = 135):         │
└─────────────────────────────────┘          │   • irrelevant articles (n = 127)     │
                │                             │   • duplicated articles (n = 3)       │
                │                             │   • reviews (n = 5)                   │
                │                             └──────────────────────────────────────┘
┌─────────────────────────────────┐          ┌──────────────────────────────────────┐
│ Articles for which full text     │          │ Articles excluded (n = 13):           │
│ retrieved (n = 23)               │──────────│ 1= insufficient information           │
└─────────────────────────────────┘          │ 12= inconsistent methods or outcomes  │
                │                             └──────────────────────────────────────┘
┌─────────────────────────────────┐
│ Articles included in the review  │
│ (n = 10)                         │
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Figure 1: flow diagram of the included studies in the systematic review

Table 1: the accuracy, sensitivity or specificity of biomarkers in detecting oral cancer in the included studies

Study	Study design	Type of cancer	Type of plasma biomarkers	Use of biomarkers	The accuracy, sensitivity or specificity of biomarkers in detecting oral cancer
13	Prospective study	OSCC	plasma hsa-miR-542-3p	For diagnosis OSCC	AUC= 0.82
8	Prospective study	GSCC	miR-223	Novel diagnostic biomarker and therapeutic target for GSCC.	AUC= 0.703 Sens. = 67.7% Spec.= 61.3%.
9	Prospective study	OSCC	miR-125b	Promising biomarker in OSCC	AUC=0.966 Sens.=89.4% Spec.= 93.5%
10	Prospective study	Oral cancer	miR196a and miR-196b	Plasma biomarkers for the early detection of oral cancer.	AUC, Sens. and Spec. of the combined of miR-196a and miR-196b were : Ac. = 0.95 Sens. = 91% Spec. = 85%
(11)	Prospective study	OSCC	TIMP3	As potential biomarker in progression of OSCC.	AUC = 0.835 Sens. =69.6% Spec.= 84.4% .
12	Prospective study	OSCC	CAIX	Non-invasive marker for monitoring OSCC progression	AUC= 0.74 Sens.= 83.6% Spec.= 54.9%
14	Prospective study	OSCC	miR-196a and miR-196a2 gene	As prognostic predictors of OSCC	Plasma miR-196a AUC=0.75
15	Prospective study	OSCC	miR-181a and miR-181b	As putative biomarker for detecting OSCC	miR-181a AUC=0.84 miR-181b AUC=0.74 Combined miR-181a and miR-181b AUC= 0.89
16	Prospective study	OSCC	miR-31	Biomarker for diagnostic OSCC	AUC =0.72
(17)	Prospective study	OSCC	miR-24	As validated marker for detection OSCC.	AUC = 0.73

AUC=   Area under carve (Accuracy)
Sens.= Sensitivity
Spec.= Specificity
OSCC= Oral squamous cell carcinoma
GSCC= Gingival squamous cell carcinoma
TIMP3= Tissue inhibitor metalloproteinase-3
CAIX =Carbonic anhydrase IX

DISCUSSION

Detection and diagnosis of different types of oral cancer in the late stage disease lead to increase of morbidity and mortality globally [10, 18], therefore the searching for good and accurate markers to detect early stages of oral cancer is essential and important in the prognosis and treatment. There are several types of biomarkers that can be employed for this purpose. The diagnostic efficacy of biomarkers based on their accuracy, sensitivity and specificity in the diagnostic oral cancer [15, 19].

The present systematic review summarized the different types of plasma biomarkers which have been reported to have pivotal role in the diagnostic different types of oral cancer. Ten studies were including in this review[8-17]. Oral squamous cell carcinoma was the most type investigated in nine articles [9-17]. It has been reported that oral squamous cell carcinoma represented about 90% of the all cases characterized with oral cancer around world [20].Plasma miRNAs were selected as biomarkers in 80% of including studies in this review. It has been estimated that about 1/3 of human genes could be regulated by miRNAs [21], furthermore miRNAs are released into body fluids as plasma and is abnormally expressed (up-expressed or down-expressed) in many diseases as cancer, therefore, miRNAs formed the majority of plasma biomarkers for detection and diagnosis many type of oral cancer. Different types of plasma biomarkers were used and their diagnostic ability varied based on the estimation of their accuracy, sensitivity and specificity in the diagnosis of patients with oral cancer [22].

Highest values of accuracy and specificity was estimated for plasma miR-125b among all plasma biomarkers which investigated in the included studies. Plasma miR-125b was reported as promising plasma biomarker for detecting OSCC. It has strong ability to differentiate OSCC from healthy controls. Plasma miR-125b expression was increasing significantly in patients with OSCC more than that in the healthy controls [9]. These results were supported by many of previous studies which confirmed using of miRNA-125b as potent and promising diagnostic biomarker for many types of cancers. Zhu et al.[23] reported that circulating miRNA-125b had ability to become a novel biomarker for early diagnosis and prognosis prediction of epithelial ovarian cancer. Also, Wei et al. [24] indicated that in their meta-analysis review, miRNA-125b could serve as potential biomarker with relatively high accuracy in the diagnosis of many human cancers. Furthermore, circulating

miR-125b was reported as novel biomarker for predicting lung cancer [25] and breast cancer [26].

On the other combination of miR-196a and miR-196b as plasma biomarkers recorded the highest sensitivity in early detection of oral cancer among all biomarkers used in included studies. Lu et al.[10] recorded in their results that miR-196a was as an excellent biomarker for detection specificity, while miR-196b for detection sensitivity and the combined use of miR-196a and miR-196b may lead to enhance the sensitivity and specificity in detection oral cancer.

From the results exhibited of all included studies in this review we can notice that many studies focused on the using plasma miRNAs as prognostic or diagnostic biomarkers for oral cancer. Plasma miRNAs could be detected in plasma rapidly and employed as accurate and sensitive biomarkers. These characters were recorded previously by Abd El-Fattah et al. [27]; they reported that miRNAs have been released into the body fluids as small quantities and could be detected rapidly and accurately. Manasa [28] showed that there was positive correlation between microRNA expression levels and clinic-pathological parameters and can be used as diagnostic and prognostic marker for oral carcinoma. In summary we can conclude that, plasma microRNAs biomarkers occupied wide scope of the included studies in this review and could be serve as potent and sensitive biomarkers (especially plasma miR-125b expression and combination of miR-196a and miR-196b) for prognostic and diagnostic different type of oral cancer.

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