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Review Article

Screening of oral squamous cell carcinoma by serum changes: A systematic review and meta-analysis

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ABSTRACT

Background: Oral squamous cell carcinoma (OSCC) is the sixth common cancer in the world and 90% of oral malignant tumors. The aim of this study was the investigation of changes in some metabolic elements of OSCC patients' serum.
Materials and Methods: In this study, international databases such as PubMed, Science Direct, Scopus, Web of Science, and National (Magiran, IranMedex) were searched from 1980 to 2019. To analyze the data, a random-effects model was used to combine the differences in the mean of studies in STATA Software (version 12).
Results: A total of 724 articles were found with initial searching that 474 duplicate articles, 228 articles were excluded by reviewing the title and abstracts, and 17 articles were excluded from the study due to lack of inclusion criteria. Finally, five articles entered the meta-analysis phase. The mean difference value for zinc concentration of blood serum was 2.01 (95% confidence interval (CI): 0.36–3.66) and for copper was 1.04 (95% CI: 0.01–2.07). In both populations, the heterogeneity was found between studies ($I^2 = 97.4$, $P < 0.001$).
Conclusion: Probably higher serum levels of copper and zinc could be one way to help to do a primary screening of OSCC in suspected patients.

Key Words: Elements, meta-analysis, mouth neoplasms, serum, squamous cell carcinoma

INTRODUCTION

More than 90% of head-and-neck cancers are squamous cell carcinoma (SCC). Oral squamous cell carcinoma (OSCC) is the sixth most common cancer in the world and 90% of all oral malignant tumors. This tumor originates from the oral dysplastic epithelial lining of mucosa. Histopathologically, it is characterized by invasion of epithelial islands and bonds composed of malignant squamous cells.[1] Despite many advances in oncology, its prognosis is still undesirable due to the aggressive nature of this tumor. This malignant tumor has a 5-year survival rate below 5% and has not improved in the last three decades.[2,3] According to the studies, the incidence of OSCC is increasing among young patients.[4-6]

Early detection of OSCC is the most important factor of prognosis. Today, various clinical and

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laboratory methods for early detection and prognosis have been proposed.[7-9] Many metabolic disorders, oral precancerous lesions, and oral cancers are associated with the changes in the concentration of some elements such as copper, iron, zinc, and magnesium in the body fluids including blood serum.[10] Biomarkers are important tools for diagnosis in different clinical stages. They are used to improve accuracy for diagnosis and prognostic stages.[11] Furthermore, deficiency of some metabolic elements has an important role in many human pathology processes.[12] Analysis of metabolic changes may be a valuable approach to understanding the biochemistry of tumors. It can be used for the detection of new therapeutic targets.[13] Biochemical changes in the serum of patients with oral cancer can help in diagnosis and prognosis of this cancer.[14] According to the studies of Kanna, Than, and Baharvand, the concentration of ferritin, copper, and zinc in blood serum is higher in patients with OSCC than in healthy people.[15-17] On the other hand, Hosthor *et al*. showed that the concentration of Fe, Mg, and zinc in these patients has decreased compared to healthy people.[18] Based on the studies, copper was the strongest predictor of OSCC among the other elements.[18,19] Serum-based clinical trials of the patients are the noninvasive method of diagnosis.[20]

However, there are many studies on the association of biomarkers and elements in the serum of patients with OSCC, but a systematic review is needed to obtain more comprehensive results. Therefore, the aim of this study was to evaluate the serum levels of some elements in patients with OSCC.

MATERIALS AND METHODS

Search methods

The present study is a systematic review was approved by the Research Ethics Committee of Isfahan University of Medical Sciences, Isfahan, Iran (with the ethics code of 397714). To evaluate some serum metabolites (iron, zinc, copper, folic acid, ferritin, homocysteine, and calcium) in patients with OSCC. The entire implementation and writing process of this study have been evaluated using the PRISMA checklist.[21] Qualitative evaluation and data extraction were done by two authors independently for bias prevention. We searched the articles with the keywords such as "Oral Squamous Cell Carcinoma," "Serum," "Calcium," "Homocysteine," "Folic Acid," "Ferritin," "Copper, "Zinc," and "Iron" in scientific search engines (Web of Science, Scopus, PubMed, Science Direct, and IranMedex as well as Magiran, and Scientific Information Database) from 1980 to January 2019.

Selection of the studies

First, the title and abstract of the identified articles were reviewed and duplicates were removed at different sites. Then, among the remaining studies, articles with inclusion criteria were included in the study. It should be noted that only original research studies were selected and studies such as case reports, brief reports, and reviews were not used.

Quality assessment of the articles

Like other meta-analysis studies in the medical sciences, we also used the PRISMA checklist. It is a standard checklist in the systematic and meta-analysis studies to evaluate the quality and reporting of the selected papers by the researcher. The checklist contains 27 items that assess different aspects of the methodology of systematic and meta-analysis studies.[21-23]

Data extraction

For ease of work, it was decided to set up a table and collect information such as author's name, year of study, sample size, and mean and standard deviation of serum metabolites in patients and healthy people.

Inclusion and exclusion criteria

Only Persian-language and English-language articles were included that reported quantitative serum SCC metabolites (iron, zinc, copper, folic acid, ferritin, homocysteine, and calcium). Exclusion criteria were lack of relevance to the main subject, lack of reporting or qualitative reporting of SCC metabolites, failure to report sample size, or lack of control of confounders. Each of these studies was investigated by two researchers in expressing results simultaneously.

Statistical analysis

The studies were combined with respect to variance, mean variables, and sample sizes of healthy and patient groups. To calculate the mean of group differences, the variance of the groups was used to weight the individual studies. Due to the heterogeneity in the studies, the random-effects model was used to combine the results of the studies. Cochran's test and I^2 index were used to assess the heterogeneity of the studies. STATA software12 (StataCorp LLC, Lakeway Drive, College Station, Texas, USA) was used for all required analyzes in this study.

RESULTS

Search results

Initial searches of national and international databases identified 724 articles. By deleting 474 duplicate articles, 250 articles entered the systematic review stage. After reviewing the title and abstract, 228 articles were removed. Finally, out of 22 articles, 17 studies were excluded due to lack of inclusion criteria. Then, five articles[15,17-19,24] entered the meta-analysis stage [Figure 1].

Meta-analyses

The studies reviewed in this meta-analysis were published between 1984 and 2017. The design of the study in all of these articles was cross-sectional. All studies were published in English. Ferritin's levels have been reported in only two studies in the patient and healthy groups.[15,17] Furthermore, the amount of iron and calcium has been reported only in the study of Hosthor *et al*.[18] Therefore, meta-analysis cannot be performed for ferritin, iron, and calcium. Instead, zinc and copper's levels were reported in four of these five articles for both the patient and healthy groups; therefore, only zinc and copper's levels were included in the meta-analysis [Table 1]. It should be noted that homocysteine and folic acid were excluded from this study due to the lack of inclusion criteria such as examination in the head and neck.

Regarding the heterogeneity of the studies (I^2 = 97.4%, P < 0.001), a random-effects model was used to estimate the mean differences of the studied variables in the healthy and patient groups and to estimate the confidence interval (CI). According to the random-effects model and combination of mean differences for zinc and copper, estimation of the mean difference of zinc and copper is shown in Figures 2 and 3. The total amount of the estimated mean difference for zinc was 2.01 (95% CI: 0.36–3.66) (I^2 = 97.4%, P < 0.001) and for copper was 1.04 (95% CI: 0.01–2.07) (I^2 = 97.4%, P < 0.001). These results showed that the amount of zinc and copper in patients with OSCC was significantly higher than the healthy people.

Risk of bias

To explain the bias of the publications in the reviewed studies, we used the funnel plot. The funnel diagram for both zinc and copper showed that the data were not symmetric [Figures 4 and 5]. Therefore, there is a publication bias in the studies, indicating that researchers are not publishing or not having access to some of the articles or results of the studies.

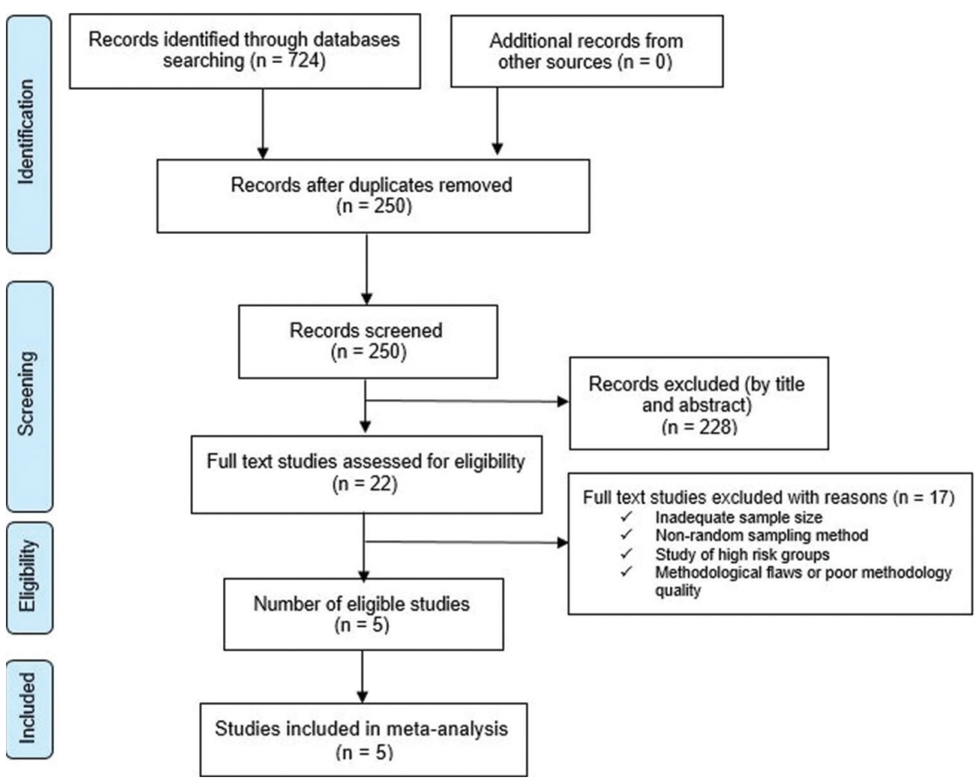

Figure 1: PRISMA flowchart for the article selection.

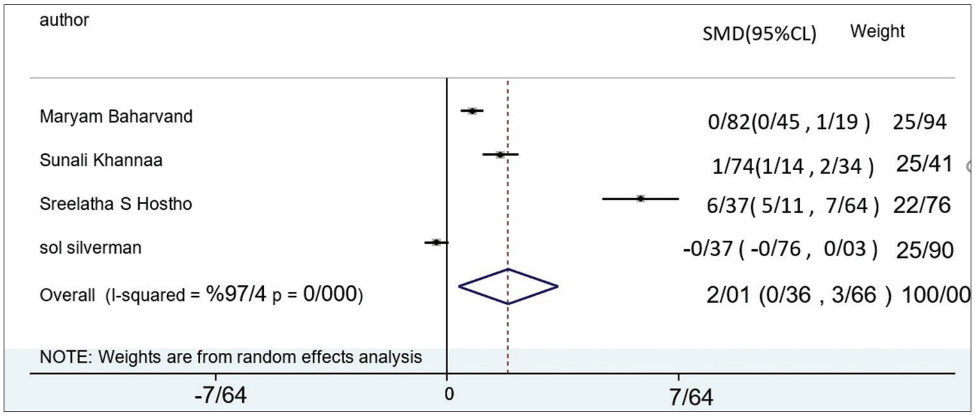

Figure 2: Mean difference of Zinc and its 95% confidence interval in studies reviewed by random-effects model. The midpoint of each segment represents the mean difference and the length of each line represents 95% confidence in each study. The rhombic sign indicates the mean difference for the patient group and the control group.

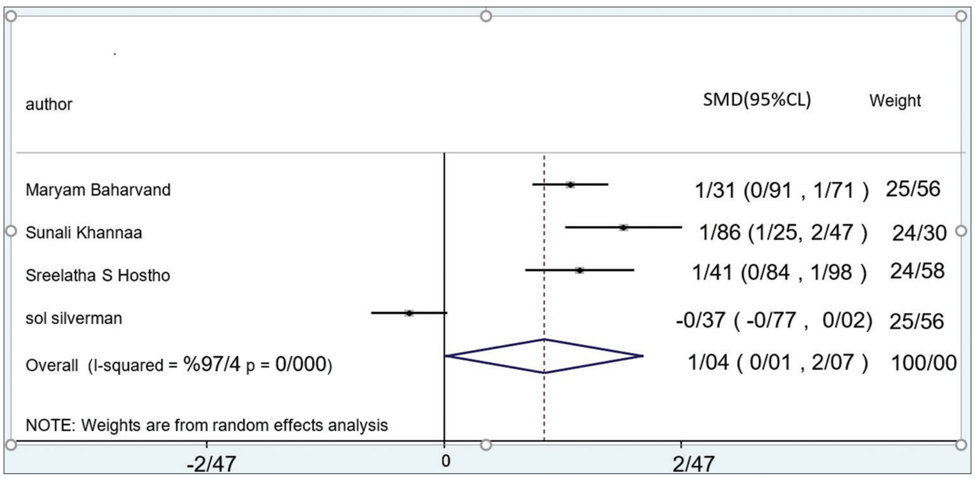

Figure 3: Mean difference of copper and its 95% confidence interval in studies reviewed by random-effects model. The midpoint of each segment represents the mean difference and the length of each line represents 95% confidence in each study. The rhombic sign indicates the mean difference for the patient group and the control group.

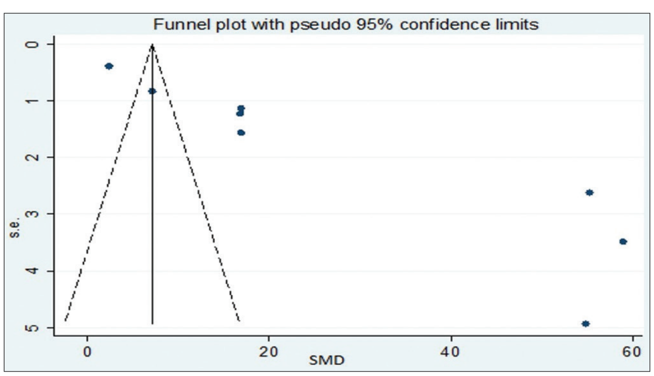

Figure 4: Funnel plot diagram of the entered studies for the zinc variable.

DISCUSSION

The present meta-analysis study aimed to evaluate the serum level changes of some elements (iron, zinc, copper, folic acid, ferritin, homocysteine, and calcium) in patients with OSCC. Most of the research in this study showed that the amount of zinc and copper in patients with OSCC was significantly higher than the healthy people. Furthermore, copper due to its oxidation and regeneration activities plays an important role in the production of the free oxygen metabolites.[25] Free radicals are able to bind to natural parts of the cell, resulting in lipid peroxidation, protein oxidation, and nucleic acid degradation.[26] Therefore, free radicals play a main role in the development and prognosis of various cancers. As a result, elevated serum copper's levels due to increased oxidation processes may increase the potential for oral cancer.[27] However, there is a contradictory study in which copper's levels in patients with oral cancer were lower than in healthy people.[24]

Zinc is one of the antioxidants in the foods that is dependent on the activity of the body's antioxidant enzymes, such as superoxide dismutase.[28] In addition, zinc directly prevents DNA damage and ultimately gene mutation.[29] In some studies, changes in the level of zinc in the serum have been observed in different types of cancers. For example, serum zinc's levels have decreased in the bladder[30] and prostate cancers[31] and increased in thyroid cancer.[32]

According to studies, long-lasting inflammation associated with oral cancer and precancerous lesions may induce oxidative stress. In addition to contributing the transcription process, zinc plays an important role in enzymatic antioxidant systems such as carbonic anhydrase, superoxide dismutase, and leucine aminopeptidase.[33,34] Baharvand *et al*. showed that zinc in patients with OSCC was close to normal range in the Iranian population, but zinc's level was lower in healthy persons,[17] which probably indicates nutritional deficiencies in the Iranian population.[35] It seems that elevated levels of zinc in patients with oral cancer may be related to their eating habits.

Conflicting to the results of this study, Prasad *et al*. showed that there are zinc deficiency and impaired cellular immunity in a number of patients with head-and-neck cancer.[36] Doerr *et al*. reported inadequate zinc in patients with head-and-neck cancer.[37] The level of ferritin and calcium in patients with OSCC was significantly higher than in the healthy people, but the level of iron in healthy people was significantly higher than in patients with OSCC [Table 1].

The main cause of hypercalcemia in patients with malignant tumors is increasing bone resorption and extracellular calcium excretion. Furthermore, the other reason of hypercalcemia is inadequate renal calcium clearance.[38] Hypercalcemia is often observed in the patients with advanced oral cancer and final stage of disease.[38] Iron deficiency in patients with cancer is known that can be due to malnutrition caused by the tumor.[38] Elevated levels of ferritin may occur in the infection, inflammation, and chronic diseases.[39] Furthermore, ferritin and iron have a role in the cancer process.[40]

CONCLUSION

Amount of ferritin, zinc, copper, and calcium in the patients with OSCC were higher than in healthy people. Furthermore, the present meta-analysis showed that serum levels of copper and zinc were significantly higher in the patients. Probably higher serum levels of copper and zinc could be help to primary screening of OSCC in suspected patients.

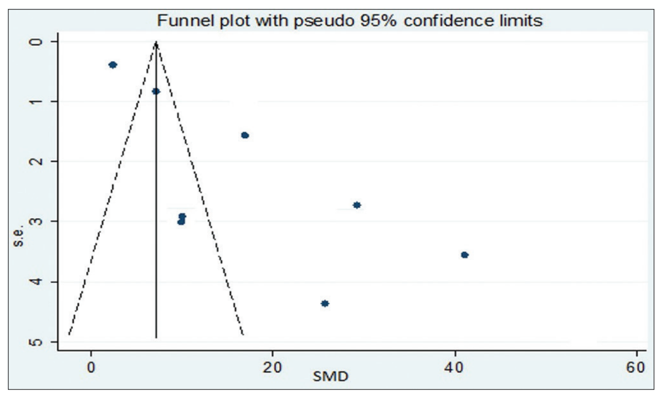

Figure 5: Funnel plot diagram of the entered studies for the copper variable.

Table 1: Characteristics of the articles on serum metabolites in patients with oral squamous cell carcinoma and healthy people

References	Years	Study deign	Serum	Healthy groups		Patient groups	
				Sample size	Mean±SD	Sample size	Mean±SD
Baharvand *et al.*[17]	2014	Cross-sectional	Ferritin	66	106.13±72.96	60	267.41±24.9
			Copper	66	114.2±38.96	60	209.85±95.68
			Zinc	66	64.5±31.5	30	113.51±52.3
Khanna *et al.*[19]	2013	Cross-sectional	Copper	30	0.88±0.22	30	1.29±0.22
			Zinc	30	1.29±0.89	30	1.48±0.8
Hosthor *et al.*[18]	2014	Cross-sectional	Zinc	30	94.2±14.25	30	40.71±6.7
			Calcium	30	0.00045±0.00973	30	0.001±0.00065
			Copper	30	122.69±16.5	30	218.17±94.48
			Iron	30	0.1154±0.26	30	0.041±0.007
Silverman and Thompson[24]	1984	Cross-sectional	Copper	21	142.6±29.1	30	132.5±25.3
			Zinc	21	85.2±12.3	30	88.74±10.36
Khanna *et al.*[15]	2017	-	Ferritin	15	0.075±0.0017	30	0.162±0.025

SD: Standard deviation

Limitations

The first limitation was the presence of OSCC diagnosis with different stages of the disease. Furthermore, we have different diagnostic methods in the studies. We did not have access to the full text of some articles.

Suggestions

It is recommended that more studies could consider for about the type of OSCC detection method. Furthermore, since all the studies reviewed in this study were cross-sectional, it is suggested that longitudinal and cohort studies will be performed to compare the rate of changes in these elements in different stages of this cancer.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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