

Estimation of Serum Micronutrient Levels and The Possible Risk Of Oral Cancer And Premalignancy

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Abstract; The oral cancer is one of the most prevalent type of cancer worldwide. It is invariably linked to lifestyle habits like alcohol consumption, cigarette smoking and poor nutritional status. This apart, the role of micronutrients in oral carcinogenesis still remains less understood. So the study was undertaken to assess the micronutrient levels of oral cancer and precancerous patients. The estimation of Haemoglobin showed there was no significant difference between controls, premalignancy cases and in cancerous conditions. Zinc and copper level levels were significantly lower in cases than in controls. There is a positive correlation between serum iron and selenium level and oral cancer patients, yet we didn't find significant increase in serum iron level either in precancerous or oral cancer patients. This study may indicate that very high or low levels of micronutrients associated with oral carcinoma. Yet moderate amount of micronutrients in diet may have protective effect on oral carcinoma which requires further research in these lines.

Keywords; Oral cancer, iron, micronutrients, copper.

I INTRODUCTION

The annual incidence rates of oral and pharyngeal cancer is very high which is around 6,15,000 globally [1]. Oral carcinogenesis is mostly associated to lifestyle habits like cigarette smoking, chronic alcohol consumption [2, 3, 4] and low dietary intake of fruits [5, 6]. A high intake of fruit and vegetables have been linked with a lower risk of oral and pharyngeal cancer, whereas a poor nutritional status and an unbalanced diet have been related to an elevated risk [2, 3, 5]. Tobacco use and alcohol consumption can result in irreparable genetic injury leading to development of the cancer [3]. However, apart from an inverse association with intake of fruits and vegetables, the role of specific foods and nutrients remain less understood [7]. Trace elements including copper, manganese, zinc, iron, cobalt, selenium, silicon, can act as either inhibitory or causative agents of cancer. [8]

There have been a limited number of epidemiologic studies of iron and oral cancer risk, but three studies found a trend in the odds ratios (ORs) with decreasing dietary intake of iron [9] and one found a non-significant association between oral premalignancy and low iron intake in Indian women [10]. In experimental studies of 4-nitroquinoline-N-oxide (4-NQO) exposed laboratory rats, the incidence of oral tumours was significantly elevated in iron deficient animals [11] although these differences were not confirmed in subsequent studies [12]. Despite these findings; the role of low iron in oral cancer is not well understood.

The two other micronutrients copper and zinc, is increasingly recognized for its possible role in the prevention and modulation of diseases. A study by Jaydeep et al proved increased level of copper in oral leukoplakia and cancer. But the level of zinc was decreased significantly in male patients with leukoplakia and cancer. [13] Zinc deficiencies impair host protective mechanism designed to protect against DNA damage, enhances susceptibility to DNA damaging agents

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and ultimately increase the risk of cancer.[14]Several studies have shown that plasma copper concentrations are increased in various carcinomas .However the level of zinc is significantly decreased in cancer group [15,16]However usefulness of the serum zinc and copper determinations in cancer prevention, detection, monitoring treatment and prognosis requires further investigations.The current study was conducted to determine whether blood iron levels and other selected serum micronutrient levels are associated with the risk of oral cancer. We also examined the micronutrient levels in 13 subjects with oral leukoplakia or keratosis, premalignant conditions that may predispose individuals to oral cancer.

II MATERIALS AND METHODS

The present analysis is based on data from a case–control study of 60histopathologically confirmed oral cancer patients, conducted from 2009 to 2010, from a major teaching hospital in Mangalore.Cases ranged between 22 and 77 years of age (median 57 years).Thirteen cases of precancerous conditions i.e. leukoplakia and Erythroplakia were also included in the study. Subjects taking medications and antioxidant supplementation were not included in the study.Controls comprised of 70 subjects, aged 20–68 years admittedto the same network of hospitals for acute, non-neoplastic conditions notassociated with smoking, alcohol or long-term dietary change. All cases and controls were interviewed using a structured questionnaire that contained questions on smoking history, alcohol consumption and occupation. Subjects signed a consent form that was approved by the Institutional ethical committee. Approximately 85% of both casesand controls who were approached agreed to participate. After the interview, the subjects were brought to a phlebotomy station for venepuncture. 5 ml of venous blood was collected, centrifuged; serum and erythrocytes obtained were then aliquoted and immediately frozen at -70⁰ until it is assayed.

Blood analysis: Serum iron was assayed spectrophotometrically by Bathophenanthroline method. [17]The Optical Density (OD) of the colour was measured in a spectrophotometer at 535 nm. Haemoglobin levels were measured in red cells and whole blood by the ferricyanide-cyanide method as an indicator of anaemia [18]. The estimation of copperwas done by Atomic absorption spectrophotometer. The concentrations of zinc in erythrocytes and plasma were measured by flameless atomic absorption spectrophotometer using a Model 460 atomic absorption spectrophotometer [19].The serum samples were assayed for selenium by neutron activation analysis [20]

III Results and statistical analysis

The data were analyzed using SPSS 16 version. Statistical comparisons were done by paired t test. Data were expressed as mean±SD.p<0.05 considered as statistically significant.

Our study had 60 oral cancer patients. The most frequent site of the tumor was the tongue (60%), floor of the mouth (22%) and other areas (18%). And case group alsoincluded thirteen subjects with oral premalignancy, out of which ten were diagnosed with leukoplakia and threewith Erythroplakia. Seventy subjects participated as controls.The estimation of Hemoglobin showed there was no significant difference between controls, premalignancy cases and in cancerous conditions and their level was within normal values. Zinc and copper level levels were significantly lower in cases than incontrols (p<0.001).There is a positive correlation between increased iron and seleniumlevel (p<0.0001) and oral cancer patients, yet we didn’t find significant increase in serum iron level either in precancerous or oral cancer patients

• **Concentrations of micronutrients in Premalignancies-Table 1**

Micronutrients	CONTROL	CASE
IRON(µg/dl)	102.9±17.48	109.8±26.43
COPPER(µg/dl)	180.9±5.48	168±6.44**
ZINC(µg/gHb)	35.6±6.25	34±5
Hemoglobin(g/dl)	14.5±1.92	14±1.92
Selenium(µg/dl)	0.10±0.01	0.11±0.08

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• **Concentrations of micronutrients in Oral cancer-Table 2**

Micronutrients	CONTROL	CASE
IRON($\mu\text{g}/\text{dl}$)	102.9 \pm 17.48	110.8 \pm 44.38
COPPER($\mu\text{g}/\text{dl}$)	180.9 \pm 5.48	109.76 \pm 25.58***
ZINC($\mu\text{g}/\text{gHb}$)	35.6 \pm 6.25	31.4 \pm 5.82***
Hemoglobin(g/dl)	14.5 \pm 1.92	13.8 \pm 2.31
Selenium($\mu\text{g}/\text{dl}$)	0.10 \pm 0.01	0.12 \pm 0.04***

Values are mean \pm SD. **p<0.01;***p<0.001

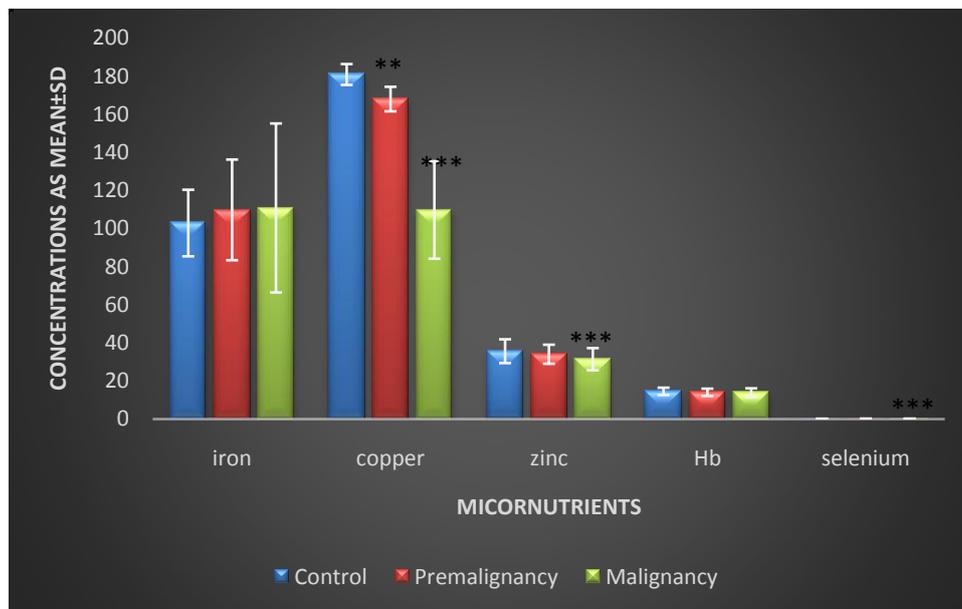


Fig 1; The level of micronutrients in premalignancies and oral cancer patients. Bars represent different micronutrients in controls, Premalignancy and in oral cancer cases, **p<0.01;***p<0.001

IV DISCUSSION

The positive association of oral cancer risk and increased serum selenium level observed in this study was unexpected and in contrast to the results from many of the previous studies [21]. The serum study conducted in patients with untreated cancer showed a significantly higher serum selenium level among cases, but the erythrocyte levels of selenium were lower among oral cancer patients [22]. Our result was consistent with a large lung cancer study in the Washington County population, which indicated a positive doseresponserelationship between lung cancer risk and prediagnostic serum level of selenium, especially among persons with low levels alpha-tocopherol [23]. These inconsistent findings in humans are in line with animal studies, in which selenium has been found to exert both cancer-inhibiting and -enhancing effects, depending on the cancer sites and carcinogens [21, 24]

The literature regarding the association between iron and oral cancer is controversial. Our findings of increased oral cancer serum iron level does match with the several of previous research findings [9,24] whereas some other studies indicated that deficiency of iron resulted in oral carcinoma [25]. One aspect of diet that has not been widely studied is iron metabolism. Iron is an essential nutrient, and iron deficiency is a very common form of malnutrition worldwide. A

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high level of available tissue iron may increase the risk of cancer through its contribution to the production of free oxygen radicals. Iron deficiency or iron excess leads to oxidative DNA damage. [9, 26]

The finding of low levels of zinc and copper associated with oral cancer patients in our study is associated with many of the research findings previously.[16,27]The copper/zinc ratio may serve as good indicator for the early detection of oral cancer. Zinc deficiencies impair host protective mechanism designed to protect against DNA damage, enhances susceptibility to DNA damaging agents and ultimately increase the risk of cancer.However, the usefulness of serum copper, zinc and other micronutrient determinations in cancer prevention, detection, prognosis and treatment require further investigations.

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