REVIEW ARTICLE

CURRENT FINDINGS ON NUTRITION AND ORAL CANCER

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ABSTRACT

Head and neck cancers are considered the sixth most common cancers in males and the tenth most common in females. The aetiology of oral cancer traditionally has been linked with different forms of tobacco use and alcohol consumption. However, other authors have reported oral cancer in people who do not use tobacco or alcohol and suggested that other aetiological factors may be associated with oral cancer development including diet and nutrition, viruses, radiation, ethnicity, familial and genetic predisposition, oral thrush, immunosuppression, use of mouthwash, syphilis, dental factors and occupational risks. World Health Organization (WHO) reports that 35 – 55% of human cancers and about 15% of oropharyngeal cancers can be ascribed to dietary deficiencies or imbalances. Foods and food groups such as fish, vegetable oil, olive oil, bread, cereals, legumes, protein, fat, fresh meat, chicken, liver, shrimp, lobster, and fibre have been associated with protective effects on oral and pharyngeal cancers. This review examines the relationship between different nutrients and nutritional factors, and occurrence and prognosis of oral cancer.

Key words: Oral cancer, Nutrition, Carbohydrates, Vitamins, Zinc

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Introduction

Head and neck cancers are considered the sixth most common cancers in males and the tenth most common in females [1]. Previous studies have reported somewhat varying incidence rates of occurrence of Head and neck cancers with the highest incidence rates reported in Southeast Asia[2, 3]. Oral cancer incidence of 2 - 4% has been reported from Europe and America [4, 5], while incidence rates of up to 40% was reported from India and Sri Lanka [6]. The high incidence rates reported from the India subcontinent is supposedly due to ubiquitous habits of chewing tobacco, betel quid and areca-nut [7].

The aetiology of oral cancer traditionally has been linked with different forms of tobacco use and alcohol consumption. Previous studies from United States[8] and Poland[9] found 75% and 82% respectively of oral cancer cases were associated with tobacco use, while Gervasio et al.[10]and Pinhort et al.,[11] found 86% and 63.9% respectively of oral cancer cases were associated with both tobacco and alcohol use. However, other authors have reported oral cancer in people who do not use tobacco or alcohol and suggested that other aetiological factors may be associated with oral cancer development including diet and nutrition, viruses, radiation, ethnicity, familial and genetic predisposition, oral thrush, immunosuppression, use of mouthwash, syphilis, dental factors and occupational risks[12, 13].

The large differences in cancer rates among countries, striking changes in these rates among migrating populations, and rapid changes over time within countries indicate that some aspect of lifestyle or environment may be largely responsible for the common cancers in Western countries[14]. World Health Organization (WHO) reports that 35 – 55% of human cancers and about 15% of oropharyngeal cancers can be ascribed to dietary deficiencies or imbalances [15,16,17]. The association between nutrition and cancers generally, has been viewed from two main perspectives; the direct carcinogenic effects of carcinogens in food and food additives, and secondly, the indirect in-vivo carcinogenic effects which are due to changes in metabolism as a result of altered dietary habits [18,19].

International Agency for Research on Cancer (IARC) has previously acknowledged that low intake of fruits and vegetables predisposes to an increased risk of cancer development, and consumption of fruit and vegetables, particularly of carrots, fresh tomatoes, and green peppers were associated with reduced risk of oral and pharyngeal cancer[16, 17]. Also, numerous other foods and food groups such as fish, vegetable oil, olive oil, bread, cereals, legumes, protein, fat, fresh meat, chicken, liver, shrimp, lobster, and fibre have been associated with protective effects on oral and pharyngeal cancers[20].

1. Carbohydrates and oral cancer

The connection between carbohydrates (CHOs) and cancer occurrence was first suggested by different physiologists in the 1920s [21]. Braunstein observed that glucose disappeared from urine of diabetic patients who developed cancers[21]. Similarly, Bierich described the accumulation of lactate in the micromilieu of tumour tissues[22] and also demonstrated that lactate was essential for invasion of melanoma cells into the surrounding tissue [21]. What is today regarded as one of the hallmarks of cancers, that is, the pathologic ability of tumour tissues to convert high amounts of glucose to lactate even in the presence of oxygen, was first described by Otto Warburg and colleagues from 1923 onwards[21]. This phenomenon, which is now referred to as Warburg effect, is in contrast to normal tissues which are known to exhibit the Pasteur effect, that is, a decrease in glucose uptake and inhibition of lactate production under aerobic conditions[21].

There is a body of evidence that dietary restriction of CHO intake may prevent cancer formation. This cancer preventive attribute of CHO restriction is thought to be achieved not only by inhibition of the carcinogenesis initiation, but also, by inhibition of cancer progression once the tumour is formed by sufficiently delaying the tumour growth in such a way that it may remain undetectable throughout the subjects lifetime [21]. Several mechanisms have been suggested by different authors to be responsible for this phenomenon of the apparent reduction in cancer incidence in subjects with low or restricted CHO consumption. First, it has been said that most malignant cells, unlike normal cells, depend on available glucose in the blood for their energy and biomass generation, and because of an apparent mitochondrial dysfunction, they are not able to metabolize significant amounts of fatty acids or ketone bodies [22]. Secondly, ketone bodies are elevated when blood glucose levels are low and ketone bodies have been severally associated with inhibition of proliferation of different malignant cells invitro[23,24]. The third and perhaps the most significant reason is the fact that chronic ingestion of CHO rich diets has been found to produce high insulin and insulin-like growth factor (IGF-1), both of which have been severally demonstrated to directly promote tumour cell proliferation [25, 26].

The Insulin / Insulin growth factor (IGF) axis individually and complimentarily play significant roles in growth and metabolism. Whilst insulin exerts its influences more on metabolism especially on short term basis, the IGF axis exerts a longer term influence on growth integration [27,28]. Most of the circulating IGF-1 are complexed with insulin-like growth factor binding proteins (IGFBP-1 through to IGFBP-6)[29,30,31]. More so, most circulating IGF-1 and IGFBPs are synthesised in the liver and are up-regulated by hormones particularly

growth hormone activities and some nutritional factors [31,32]. The IGFBPs act counteractive to IGF-1 both by binding IGF-1 and by directly inhibiting target cells. The presence of IGFBP proteases in tissues enhances the activity of IGF-1 by cleaving IGFBP, thus increasing the concentration of free IGF-1[31]. The biological activity of IGF-1 is thus modulated by a complex interplay of circulating IGF-1 and IGFBP, and by local production of IGF, IGFBP and IGFBP proteases.

Aside from the IGF-1, there exists IGF-2 which has a 62% similarity to IGF-1 in its amino acid sequence and exhibit similar properties and effects to IGF-1 [31,33]. IGF-1 and IGF-2 have severally been demonstrated to have mitogenic and anti-apoptotic properties and both have been known to regulate cell proliferation and differentiation. Though the concentration of IGF-2 in blood circulation is much higher than IGF-1, IGF-2 is believed to play a less important role in post natal growth and mutagenesis when compared with IGF-1[33].

Previous studies have shown that clinical conditions with increased production of IGF-1 were associated with increased risk of cancer development[34]. Jenson et al had previously shown that colorectal neoplasia found during colonoscopy were much higher in acromegaly patients when compared with normal population[35,36]. Acromegaly is a condition characterized by excessive production of growth hormone and IGF-1[34]. Also, many studies have shown a positive correlation between IGF-1 and many others types of cancers[37, 38, 39]. IGF-I and IGF-2 were found in invitro studies to be strong mitogens for a wide variety of cancer cell lines, including sarcoma, leukemia, and cancers of the prostate, breast, lung, colon, stomach, esophagus, liver, pancreas, kidney, thyroid, brain, ovary, and uterus[40, 41, 42]. In the same vain, many studies examining the serum levels of IGF-1 and IGFBP-3 have consistently found a positive correlation between circulating serum IGF-1 and IGFBP-3 and the risk of a variety of cancers[32,43,44].

On the other hand, studies examining the relationship between IGF-I and IGF-2, and IGFBP-3 and oral cancer have been somewhat inconsistent. Xu Zhi et al[45] in a study from Poland concluded that there was no change in the level of expression of IGF-1 and IGF-2 in Head and neck squamous cell carcinoma (HNSCC) cases (Figs 1 and 2) studied in a selected population, but there was evidence for up regulation of IGFBP3 in HNSCC patients when compared to healthy population.

Fig 1: OSCC of the tongue in a middle age man

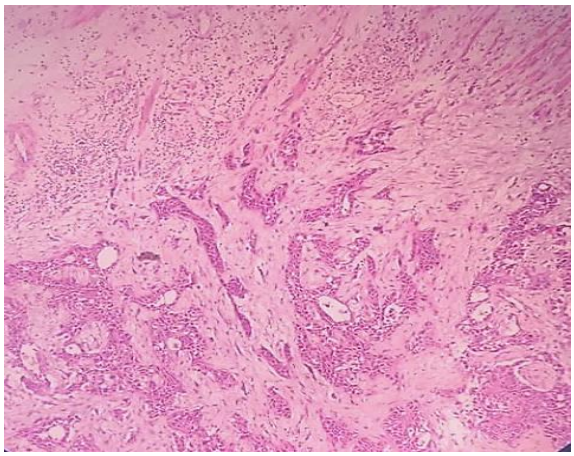

Fig 2: Photomicrograph of OSCC showing islands and strands of malignant squamous epithelial cells in connective tissue (H&E x40).

Also, Brady et al[46] using Reverse transcriptase PCR, immunohistochemistry and western blot found IGF-1 mRNA was only detected in normal cells, whereas IGF-2 and IGF-1R mRNA transcripts were highly expressed in tumour cell

lines and tissues. On the contrary, Schiegnitz et al found that serum levels of IGF-1 and IGFBP-3 were significantly lower in oral squamous cell carcinoma (OSCC) patients than in control subjects and OSCC patients with an IGF-1 serum value < 130 ng/mL showed a significantly lower survival rate compared to OSCC patients with an IGF-1 serum value ≥130 ng/mL (p=0.043) [31,47]. Brady et al [46] reported that mean IGF-1 and IGFBP-3 levels were significantly lower in cancer patients than controls (85.3 ng/ml and 2008 ng/ml versus 191 ng/ml and 2935 ng/ml, P<0.001).

2. Protein and Oral Cancer

The evidence for the relationship between cancer and protein diets is usually linked with meat consumption. Meat consumption, especially processed meat has been associated with a diverse group of cancers including colorectal cancer, stomach cancer and less strongly with breast, endometrium and prostate cancers[48]. In a previous prospective cohort study examining the association between red and processed meat, it was found that there was a 24% increased risk for colorectal cancer with red meat consumption of 62.5 g/1,000 kcal and a 20% increased risk with processed meat consumption of 22.6 g/1,000 kcal among both males and females[49]. Previous studies by Cross et al[48] showed that higher consumption of meat was positively associated with risk of cancer of the lung, liver, esophagus, and pancreas. In the same vain, Secchi et al.[50] found that there was a significant association between red meat consumption and OSCC occurrence. Other studies also showed that there was a positive association between high processed meat consumption and incidence of OSCC [50, 51].

The link between meat intake and cancer occurrence may be somewhat explained by the fact that people with high meat intake also have a high-energy or high-fat diet as part of a "westernized diet"[50]. However, it has been suggested that potentially carcinogenic effects of compounds such as N-nitroso compounds, heterocyclic amines and polycyclic aromatic compounds found in meat may be more significant in this pathway. It has been hypothesized that these compounds and others such as salts, nitrates, nitrites, Haem iron, saturated fat, estradiol present in meat may promote carcinogenesis by increasing DNA synthesis and cell proliferation, increase insulin like growth factors (IGF), affect hormone metabolism and promote free radical damage [48, 52].

In contrast to the positive association between meat consumption and cancer risk, fish consumption has been negatively correlated with the risk of developing diverse kinds of cancers[53]. It is believed that the apparent preventive ability of fish in relation to cancers may not be unconnected with the saturated fatty acid constituents. Fish and fish oil are rich sources of n–3 fatty acids and the fat-soluble vitamins A and D [53, 54]. The n-fatty acids in fish are important component of cell membrane and have been shown to have anti-inflammatory effects [55]. Similarly, n-fatty acids have been found in previous invitro studies to inhibit breast, colon and prostate cancer growth. Fernedez et al[53] found a consistent protective effect of fish consumption with colon, rectum, stomach and oral cavity cancers (OR= 0.6, 0.5, 0.7 and 0.5 respectively). They concluded that consumption of even relatively small quantities of fish may reduce the risk of several cancers including oral cancers.

3. Fats and Oral cancer

The association between dietary fat intake and several cancers was assumed because of the variations in different cancer rates worldwide, and thought to be linked with per capital fat consumption with an apparent increased incidence of most cancers, in westernized countries that have a relatively high per capital fat consumption [14]. More so, dietary fats have been shown to promote tumours in several animal models. However, studies that sought to identify dietary fat from total energy in causation of cancer have found either weak or no correlation between dietary fat consumption and cancer incidence [14, 56]. In the same vain, different correlations have been observed between animal fats and vegetable fats [57]. Many previous epidemiologic reports have found inconsistent correlation between fat

consumption and different types of cancer, probably because of the effects of many confounding factors in this association. Factors such as exercise, other dietary components of food and the type of fat (polyunsaturated, mono-unsaturated), may make it somewhat challenging to show direct correlation between fat consumption and cancer incidence [14].

Toporcov et al. [58] in a study in Brazil using 70 oral carcinoma cases and 70 matched controls observed that habitual intake of foods rich in animal and saturated fats was significantly associated with risk for oral cancer occurrence. Similarly, Franceschi et al. [59] in a study in Italy, found that consumption of saturated fatty acids was directly associated with oral cancer (OR= 1.4). Greenwood et al. [60] also affirmed the fact that increased dietary fat intake is a risk factor for oral cancer, and suggested that possible mechanisms that fatty acids may induce carcinogenesis may include increased lipid peroxidase, alteration of hormone levels, particularly oestrogen, and impairment of nutrient metabolism. Other authors have opined that fats have a modulating effect on carcinogenesis by altering the membrane fatty acid of normal and neoplastic cells and thus modifying physical-chemical environment of hormone receptors and/or enzymes of the tumour cells [61].

4. Micronutrients and Oral cancer

A. Vitamins

High fruits and vegetables consumption have been severally linked with lower risks of diverse kinds of cancer. Many studies in the 1990s showed that fruits and vegetables consumption were beneficial in the prevention of cancers. A WHO and the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) report in 1997 showed that the preventive effects of high fruit and vegetable consumption against cancer risk were convincing, showing at least a 20% reduction in total cancer risk with ≥400 g/d of fruit and vegetable intake [62]. However, most of these studies that showed strong links between fruits and vegetables consumption and cancer prevention were case control studies. Prospective cohort studies have shown weaker associations, and the 2007 WCRF/AICR report downgraded the level of evidence for several cancer types from convincing to probable, limited, or suggestive [62- 64].

The protective effects of fruits and vegetables against cancers are thought to be due to a diverse group of bioactive substances that they contain including carotenoids, vitamins C and E, selenium, folic acid, b-carotene, lycopene, dithiolethiones, indoles, isothiocyanates, flavonoids, allium compounds, isoflavones, protease inhibitors, and dietary fibers. These substances have a range of effects that are beneficial in preventing cancers including antioxidant activity, modulating the detoxification enzymes, stimulating the immune system, transferring the methyl groups in the DNA methylation, modulating steroid hormone metabolism, and anti-proliferative effects [62, 65]. Also, some studies have shown that DNA adducts, which are a reliable indicators of genotoxic damage, are significantly and inversely correlated with the intake of β-carotene and vegetables [66].In a study in Italy, the relationship between consumption of some selected foods and oral cancer was analysed and consumption of milk, meat, cheese, carrots and fruits and vegetables were found to be inversely related to oral cancer occurrence but the most significant protection against oral cancer was found with frequent fruit consumption [67].

In a meta- analysis using 15 case control studies and one cohort study, Pavia et al[68] showed that each portion of fruit consumed per day significantly reduced the risk of oral cancer by 49%, while for vegetable consumption, the meta-analysis showed a significant reduction in the overall risk of oral cancer of 50%. In a previous study from Nigeria[69] we reported that low consumption of fruits and vegetables were associated with increased risk of oral cancer, although the risks were not statistically significant. It was reported in another study[70] that serum Vitamins A, C and E were significantly lower in oral cancer cases when compared with control cases, and the risk of oral cancer was 10.89, 11.35, and 5.6 times more in

patients with low serum vitamins A, C, and E, respectively.

B. Iron

Anaemia is the most common micronutrient deficiency, affecting approximately 24.8% of the general population; with an estimated 1.62 billion people affected. Iron deficiency anaemia (IDA) is the most common form of anaemia, accounting for about 50% of all cases of anaemia [71]. Previous studies have associated IDA with increased risk of oesophageal, gastric and colon cancers[72-74]. It has been observed that iron contribute to almost all aspects of tumourgenesis such as tumour initiation, microenvironment, and metastasis[75]. IDA may cause the impairment and or deraignment of molecular and metabolic functions of cells; by causing mitochondrial dysfunction. Also, cells with iron deficiency (ID) undergo apoptosis inhibition, genomic instability and aging, and ID-induced reduction in nitric oxide synthase activity, resulting in DNA damage, oncogene activation, DNA repair enzyme inhibition, and macrophage antitumor activity down regulation [75].

One of the earliest suggestions that nutrition may play a role in aetiology of oral cancer comes from studies in Sweden that found a link between Iron deficiency anaemia (Plummer-Vinson syndrome) and pharyngeal cancer in women [76]. Gupta et al. [77] in a study in India had reported that there was a 2.5 fold increase in the risk of oral precancerous lesions in women in the lowest quartile of iron intake compared with other women. Similarly, Jayadeep et al[78] reported that oral cancer patients had a significantly lower serum iron compared to those with normal controls and those with oral leukoplakias.

Ironically, some studies have suggested that excess iron in body stores could predispose to cancer. Edling et al. [79] and Grinsrud et al. [80] have in separate studies found that workers in iron ore mining and pig iron department respectively had high levels of serum iron and increased risk of lung cancer. It has been suggested that Iron binding sites on macromolecules can serve as centres for repeated production of hydroxyl radicals generated via the Fenton reaction thus causing DNA damage [81]. Furthermore, iron together with oxygen could form a mixture that leads to increased production of free radicals. It has also been suggested that the presence of iron salts can decrease the protective effect of natural antioxidants like vitamin E, and thus contribute to carcinogenesis [82].

C. Zinc

The significance and essentiality of Zinc to humans was first enumerated some 45 years ago. Zinc is an essential element that is integral to many proteins and transcription factors, which regulate key cellular functions such as the response to oxidative stress, DNA replication, DNA damage repair, cell cycle progression, and apoptosis [83]. Zinc improves cell mediated immunity and also function both as an antioxidant and anti-inflammatory agent. Zinc deficiency has been noted to result in growth retardation, hypogonadism in males, cell-mediated immune dysfunctions, and cognitive impairment. Zinc is said to be co-factor in about 300 enzymes some of which are crucial in the host defence against initiation and progression of cancer [83, 84].

Previous studies in animals have shown that administering zinc may slow down induced tumour progression [85]. Also, administration of zinc with other micronutrients have shown some therapeutic effects in patients with oral precancerous lesions [85, 86] (Fig 3). On the contrary, Petridou et al. [87] showed that there was no statistically significant difference in the daily consumption of zinc between oral cancer patients and matched controls (p=0.25). TJ Key et al[89] had classified zinc under nutrients that have insufficient level of evidence in decreasing the risk of cancers.

Conclusion

This review has shown that there are links between various nutrients consumption of an individual and oral cancer incidence. The strength of the association of the various nutrients is usually difficult to ascertain and controversial for many reasons. The complex interactions of these nutrients working to enhance or counteract the positive and or

negative effects of other nutrient are usually difficult to measure and ascertain. More so, the effects of co-factors and modifying factors such as alcohol and tobacco use, exercise, genetics and sometimes even the method of preparation of the nutrients can enhance, antagonize or modify the several effects of these nutrients in carcinogenesis. The preventive and causative effects of various nutritional factors in cancers generally, and in oral cancer particularly, will continue to be an interesting and controversial subject for further investigations even for some time come

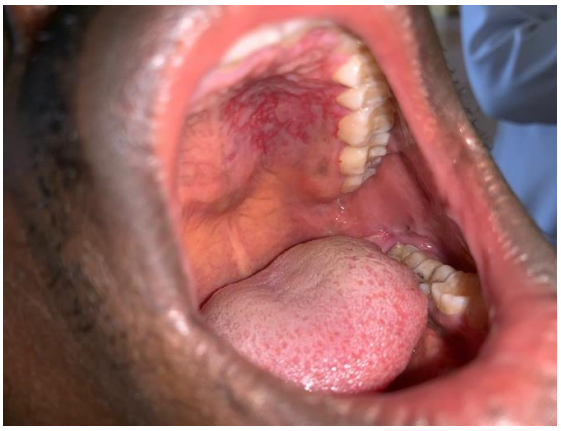

Fig 3: Oral Premalignant lesion (Erythroplakia) in the palate of 26 year old male.

Conflict of Interest: None declared

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