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Review Article

Dentistry Section

Folate Mediated One Carbon Metabolism in Head and Neck Squamous Cell Carcinoma: A Systematic Review

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ABSTRACT

Introduction: Head and neck cancer (HNC) is one of the most prevalent cancers of upper aerodigestive tract, with squamous cell carcinomas accounting for the majority of cases. Vitamin B such as folate has been associated with carcinogenesis. Folate is essential for one carbon metabolism, which involves the transfer of one carbon units for Deoxyribonucleic Acid (DNA) and Ribonucleic Acid (RNA) production, amino acid metabolism and methylation.

Aim: To evaluate the association of folate mediated One carbon metabolism with Head and Neck Squamous Cell Carcinoma (HNSCC).

Materials and Methods: For this systematic review, electronic bibliographic databases search of PubMed, Google Scholar and Scopus was done. The electronic search was performed between 15-30 November 2020 by two researchers independently. All original research, observational studies, full text articles, in which blood samples or questionnaires or both, focused on the assessment of folate mediated one carbon metabolism in HNSCC, published upto November 2020 were reviewed. Four studies published from 2005-2019 were included in which three studies were case-control and one study was a comparative cross-sectional study. This systematic review was carried out by two reviewers, using Preferred Reporting Items for Systematic reviews and Meta Analyses (PRISMA) checklist and the New Castle Ottawa Scale (NOS) for quality assessment.

Results: In this systematic review, total of four studies included, had 1504 HNSCC patients and 2970 controls. One study was reported from Nigeria, one from the European countries, one from Japan, and one from the United States of America (USA). One study had a quality score of 8 whereas three studies had quality score of 7, considering all the four studies included are of good quality.

Conclusion: Significant low levels of serum folate was present in HNSCC when compared to controls. Serum folate levels can differ due to tumour growth and subsequent metabolic changes, or they may precede and accelerate tumour progression.

Keywords: Cancer metabolism, Folic acid, New castle ottawa scale, Quality score

INTRODUCTION

Head and Neck Cancer (HNC) are one of the most common cancers. In 2018, there were 890,000 new cases and 450,000 mortality [1,2]. HNC most commonly affects the upper aerodigestive tract, the majority of which are Head and Neck Squamous Cell Carcinoma (HNSCC) [3]. HNSCC is the sixth most common cancer and the seventh major cause of cancer-related deaths globally [4]. Accounting for over 90% of all HNC [1]. Although, HNSCC is common in the sixth to the seventh decade of life, it is also reported in younger age groups in countries like India, China, the United States, and Europe [5-8]. In patients under the age of 40, HNSCC has an incidence rate of 0.4-3.6%. It mostly affects the oral cavity, oropharynx, larynx and hypopharynx [1].

Tobacco chewing, alcohol drinking and smoking are the main risk factors for Oral Squamous Cell Carcinoma (OSCC). Poor dental hygiene, a poor diet, immunosuppression, excessive sun exposure, submucous fibrosis, gastrointestinal reflux, various hereditary syndromes, chronic iron deficiency anaemia, and so on are all risk factors [1]. Recent surveys have indicated a substantial link between non smoking OSCC cases and Human Papillomavirus (HPV) [9,10].

Vitamin B are a group of water soluble vitamins that are found in green leafy vegetables, meat, eggs, dairy products, legumes, organ meats like liver, etc. Vitamin B, such as folic acid, vitamin B2, pyridoxine, vitamin B12 and choline, are known to regulate One Carbon Metabolism (OCM) and thus play a role in carcinogenesis and development. Dysregulation of 1-carbon metabolism and Deoxyribonucleic Acid (DNA) methylation is believed to promote carcinogenesis and progression. For 1-carbon metabolism, the diet provides a substantial number of necessary substrates and cofactors. As a result, it is critical to investigate the links between OCM related vitamins and cancer risk [11].

In OCM, a carbon unit is transferred from methyl donor nutrients to DNA for synthesis and methylation. Dietary inconsistencies or deficits in nutrients important for OCM can impair DNA replication, repair and regulation, thereby promoting cancer development [12].

Folate is necessary for OCM, which includes transfer and use of the 1 Carbon (C) unit for DNA and Ribonucleic Acid (RNA) production. After entering the one carbon cycle, Tetrahydrofolate (THF) receives a 1C unit from serine to produce methylene THF, a folate cofactor. 5,10 methylene THF is converted to 5-methyl THF by 5-methyltetrahydrofolate reductase (MTHFR). In the synthesis of nucleic acids, this is the 1C donor, which is used by thymidylate synthetase to convert deoxyuridine to deoxythymidine for pyrimidine biosynthesis or to various folate cofactor forms for purine biosynthesis. Later, Adenosine Triphosphate (ATP) activates methionine to produce S-adenosylmethionine (SAM), a universal methyl donor that donates its methyl group to over 100 methyltransferases involved in the control of DNA methylation, protein, neurotransmitters and membrane phospholipids. To conclude, the necessary interaction of folate with Vitamin B12, Vitamin B6, and riboflavin is required for optimal folate functioning within the one carbon cycle. Folic acid metabolism can be hampered by low levels of certain B vitamins or mutations in associated genes [13].

So, the aim of this systematic review is to evaluate the association of folate mediated One carbon metabolism with HNSCC.

MATERIALS AND METHODS

The literature searches involved PubMed, Google Scholar and Scopus. All studies with no date restriction till November 2020

which were in English only were included. The electronic search was performed between November 15-30 November 2020 by two researchers independently at Sinhgad Dental College and Hospital, Pune, Maharashtra, India. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14] (www.prismastatement.org) was used to conduct this systematic review.

Inclusion criteria: All original research, observational studies, full text articles, in which blood samples or questionnaires or both, focused on the assessment of folate mediated one carbon metabolism in HNSCC, published upto November 2020 were included in the review.

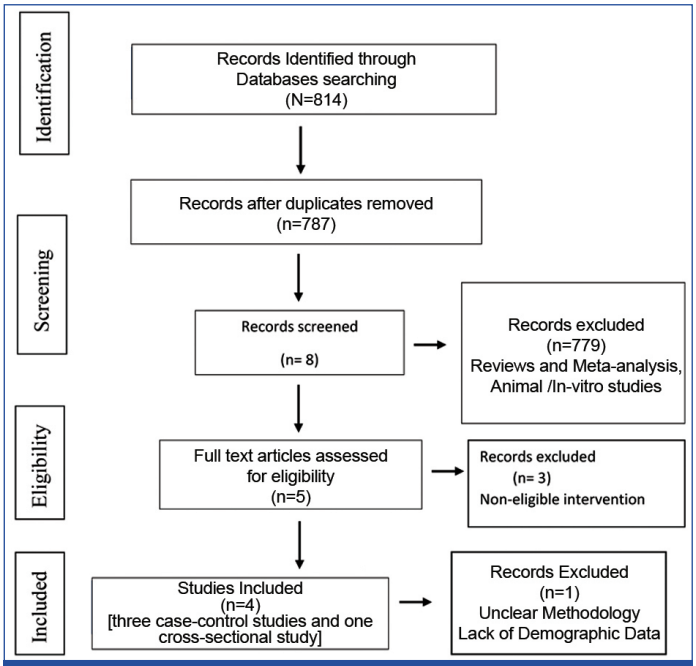
Exclusion criteria: Review articles, articles with only abstracts, and folate mediated one carbon metabolism in other cancers were excluded.

Search Strategy

Electronic searches: Searches were conducted from Medical Subject Headings (MeSH) used by the National Library of Medicine. The following keywords were used in various combinations in the search strategy in PubMed, Google Scholar, and Scopus:

One carbon metabolism [MeSH], Single carbon metabolism [MeSH], Folate [MeSH], Folic acid [MeSH], Head and neck squamous cell carcinoma [MeSH], Head and neck cancer [MeSH], Head and Neck Carcinoma [MeSH] with Boolean operators (OR, AND) to combine searches. The same keywords were used in other search platforms.

The summary of study searches is given in the PRISMA flowchart [Table/Fig-1].



[Table/Fig-1]: PRISMA 2009 flow diagram.

Data collection: The relevant data from included publications were collected in data extraction files. Two reviewers assessed titles, abstracts and full text and if there was a difference in opinion, the disagreement among reviewers was re-examined and decisions were made in a consensual manner. Each reviewer initially determined whether a study was eligible for inclusion in the systematic review based on the given criteria. The extracted data for all studies included in the systematic review are shown in [Table/Fig-2] [3,4,12,15].

Quality evaluation: One author rated the quality of each included study using Newcastle-Ottawa Quality Assessment Scale (NOS) [16]. NOS contains 8 items within 3 domains and the total maximum score is 8. Possible total points are 4 points for Selection, 1 point for comparability, and 3 points for outcomes. Studies with scores ≤4 were considered as low quality and had a very high risk of bias, 5-6 were considered as a fair quality and have a high risk of bias, whereas ≥7 were considered as good quality with a low risk of bias.

Since, the results in all these studies were not comparable, quantitative assessment (Meta-analysis) couldn't be done.

RESULTS

The [Table/Fig-2] presents the collected data of all 4 studies included. The studies were published from 2005-2019 and included 1504 HNSCC patients and 2970 controls. One study was reported from Nigeria, one from the European countries, one from Japan and one from the United States of America (USA) [3,4,12,15].

Among all the included studies, three studies were case-control and one study was a comparative cross-sectional study [Table/Fig-2]. Qualitative assessment of the included studies was done using the Newcastle-Ottawa Quality Assessment Scale (NOS). The [Table/Fig-3] shows the assessment of the quality of these studies. According to the NOS criteria, one study had a quality score of 8 whereas 3 studies had 7, considering all the four studies included were of good quality [Table/Fig-3].

DISCUSSION

In the Indian population, HNC is accountable for 30% of all cancers. HNSCC accounts for more than 90% of all HNCs [4]. Tobacco and alcohol are the main aetiological factors globally. Other causes include genetic predisposition, nutritional deficiencies and the occurrence of certain viruses [3]. The diet is one of the most important modifiable factors of cancer risk, with a variety of bioactive components, such as vitamins and essential minerals, that are protective at various stages of cancer, thus the theory of chemoprevention [3]. Fruits and vegetables are important sources of a few B-vitamins, choline, betaine, methionine, etc which are required in OCM [12].

Folate metabolism is a part of OCM, which is a universal metabolic process that activates and transfers 1C units for purine and thymidine synthesis and homocysteine re-methylation. Folate deficiency is thought to affect DNA repair and alter DNA methylation, thus increasing cancer risk, both of which can result in protooncogene activation [3].

The non covalent addition of a methyl group to DNA causes a change in gene expression without changing the base arrangement. Several dietary components have been shown to influence DNA methylation and cancer risk. The supply of donor methyl groups and as a result, the metabolic pathways of methylation activities are influenced by the OCM pathway. Many nutrients have been linked to cancer susceptibility and are thought to play a role in the etiopathogenesis of cancer [3].

Akinmoladun VI and Arinola OG, conducted a study that included 30 diagnosed cases of HNSCC and 30 healthy volunteers as controls with matched gender and age. In this study, levels of serum folate and vitamin A were decreased in cases when compared to controls. HNC was linked to tobacco and alcohol use, but not to a family history of cancer or to alcohol use alone [3].

Fanidi A et al., conducted a study that included 516 HNSCC cases and 516 individually matched controls, as well as 479 additional unmatched controls which formed control group 2 that contributed to unconditional and stratified risk analyses and measurements of serum levels of B2, B6, folate (B9), B12, total homocysteine and methionine. High levels of folate were associated with a lower risk of developing cancer. {Odds Ratio (OR) Q4 vs. Q1 0.63, 95% CI 0.35-1.16, p-value=0.02} [12].

A case-control study conducted by Suzuki T et al., involved 237 cases of HNSCC and 711 age and sex matched controls. Low dietary intakes of carotene, vitamins C and E and folate were found among the cases and were inversely associated with HNSCC

S. No.	Author/Year	Location	Study design	Total sample size	Sample size	Result	Conclusion	Total quality score
1.	Akinmoladun VI and Arinola OG [3] 2019	Nigeria	Cross-sectional study	60	30-cases 30-controls	Serum vitamin B, B2, B6, and homocysteine levels in the blood were lower in test cases, but not substantially different from controls. The cases, on the other hand, had considerably lower median blood Vitamin A and folic acid levels.	When compared to controls, the authors found that the study group had significantly lower levels of vitamin A and folic acid. This could be due to tumour growth and subsequent metabolic changes, or they could precede and accelerate tumour progression.	7
2.	Fanidi A et al., [12] 2015	European countries	Case-control study	1511	516-cases 516-Matched controls 479-Unmatched controls	The authors conducted the risk analyses of HNC and ESCCs. When factors like education, alcohol intake, smoking status, and cotinine were taken into account, study participants with higher homocysteine levels had a higher risk of developing HNC. Higher levels of folate were also linked to a lower risk. The plasma levels of the various biomarkers showed a weak or no correlation with the risk of ESCC. (p-value >0.06).	The authors concluded that individuals with low folate levels are more likely to develop squamous cell carcinoma of the head and neck.	7
3.	Suzuki T et al., [15] 2007	Japan	Case-control study	948	237-cases 711-controls	The effect of dietary folate on HNSCC risk is demonstrated in this study. Results were inversely significant (p-value=0.02)	When alcohol consumption, tobacco smoking, and folate intake were combined, with association of One Carbon Metabolism (OCM)-related gene polymorphisms (MTHFR C677T and A1298C, MTR A2756G, MTRR A66G, and TS VNTR) and the risk of HNSCC, authors found that: (1) HNSCC risk is inversely proportional to folate intake; (2) there is no significant effect of polymorphisms on HNSCC risk.	8
4.	Zhang Z et al., [4] 2005	United States of America (USA)	Case-control study	1955	721-cases 1234-controls	The subgroups of 50 and 50-64 years men, ever smoking, ever drinking and patients with pharyngeal or laryngeal cancer have a higher risk associated with 1-6 variant alleles.	Polymorphisms of the cytosolic serine hydroxymethyltransferase (SHMT1) gene which is involved in folate dependent, OCM are linked with SCCHN risk as concluded by authors.	7

[Table/Fig-2]: Comparative Description of studies included in the review and their quality score [3,4,12,15].
MTR: 5-Methyltetrahydrofolate-homocysteine Methyltransferase; MTHFR: 5-methyltetrahydrofolate reductase; MTRR: 5-Methyltetrahydrofolate-Homocysteine Methyltransferase Reductase; TS-VNTR: Thymidylate synthase-variable number tandem repeat; SCCHN: Squamous cell carcinoma of the head and neck

Studies	Selection				Comparability	Exposure			Total quality score
	Is the case definition adequate?	Representative-ness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Akinmoladun VI and Arinola OG, (2019) [3]	1	1	1	1	0	1	1	1	7
Fanidi A et al., (2015) [12]	1	1	1	1	1	1	0	1	7
Suzuki T et al., (2007) [15]	1	1	1	1	1	1	1	1	8
Zhang Z et al., (2005) [4]	1	1	1	1	0	1	1	1	7

[Table/Fig-3]: Assessment of quality of studies [3,4,12,15].

risk (p-value=0.02) [15]. The study conducted by Zhang Z et al., included 721 patients with newly diagnosed SCCHN and 1234 cancer free control subjects. They concluded that cytosolic serine hydroxymethyltransferase (SHMT1) gene polymorphism involved in OCM is associated with HNSCC risk. Levels of folate were significantly low among the cases [4]. These results suggest that low serum folate levels may play a role in multi-step carcinogenesis in the head and neck region.

The present systematic review suggested that a high intake of folate, was significantly associated with a decreased risk of HNSCC. All four studies reported in the present systematic review demonstrated that serum folate levels in patients affected by HNSCC were significantly lower than healthy controls.

Limitation(s)

Quantitative assessment (Meta-analysis) was not done in the present study, as the results of included studies were not comparable.

CONCLUSION(S)

The results in this systematic review indicate a significant association between low folate levels and increased HNSCC risk as statistically significant low levels of folate were found in the study groups when compared with the controls. Decrease in serum folate levels might also be the result of tumour development and consequent metabolic alterations in addition to the role in preceding and promoting tumour progression.

More reviews including more studies and meta-analysis are required to validate the results of this systematic review.

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