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Evaluation of folate levels in patients of lung carcinoma

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Abstract--Introduction: Lung cancer is the leading cause of cancer death globally. It is the malignant lung tumor with numerous histological variants. Due to the increasing number of tobacco smoking it is the major risk factor for lung cancer. Two main types of Lung cancer are Non-Small cell lung carcinoma (NSCLC) and Small cell lung carcinoma (SCLC). Folate is a water-soluble natural form of vitamin B9. It plays important role in homocysteine metabolism. Its decreased level may be associated with various cancers as is linked with altered DNA methylation and synthesis, and disruption of DNA repair activities. Aims: The present study was planned to evaluate the Serum Folate levels in patients diagnosed with lung carcinoma and to explore the association of increased serum folate levels with lung carcinoma patients. Materials & Methods: Fifty patients diagnosed for lung carcinoma were enrolled according to the inclusion criteria for the study. Fifty age and sex matched healthy individuals constituted the control group. Serum folate levels were estimated for all enrolled subjects. Results obtained were compared statistically among the lung carcinoma and healthy control groups. Results: Age of the study group and control group were comparable. Mean Folate levels among lung cancer patients and control groups were statistically significant. Conclusion: Lung carcinoma patients were found to have relatively

low serum folate levels as compared to control group. Lower serum folate concentrations may be associated with a higher risk of lung cancer diagnosis. More studies are needed to draw a conclusion.

Keywords---Tobacco Smoking, Histological Variants, S. Folate, Lung Carcinoma.

Introduction

Lung carcinoma is a leading cause of death worldwide and is a malignant lung tumour with numerous histological variants. These variants arise from different cell types (such as bronchial epithelium, bronchioles, alveoli, or bronchial mucous glands).¹ Tobacco smoking is the major risk factor for lung cancer. Globally, there are more lung cancer cases and deaths since 2011. With number of smokers raised between 1980 and 2012, lung cancer rates are growing in emerging countries in conjunction with tobacco smoking.²

Lung carcinoma pathogenesis involves the accumulation of genetic and epigenetic alterations that results in impairment of function of key oncogenes, tumor suppressor genes, and DNA repair genes.^{3,4} DNA methylation is an epigenetic modification. It is critical for gene regulation and development. It may result in the silencing of tumor suppressor genes and chromosome instability in tumors.⁵ Aberrant methylation (most common molecular lesion of the cancer cell), including gene-specific hyper-methylation, has also been indicated as an early event in carcinogenesis and progression of lung cancer.⁶

Folate plays a vital role in one-carbon transfer. It involves remethylation of homocysteine to methionine, which is a precursor of S-adenosylmethionine, the primary methyl group donor for most biological methylations, including DNA. Its deficiency is associated with altered DNA methylation and synthesis, and disruption of DNA repair activities. This may be the causal molecular mechanism for the relationship between folate concentration and cancer risk.⁷ Folate metabolism is influenced by its dietary intake, absorption and regulated by numerous enzymes.⁸

The methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MTR) and methionine synthase reductase (MTRR) are important enzymes involved in DNA synthesis and the generation of S-adenosylmethionine (SAM)—a universal methyl-donor for methylation reactions.⁹ Several reports suggested that genetic polymorphisms in these genes can be associated with lung cancer risk¹⁰⁻¹³, which may be modulated by folate intake.^{14,15} The study is planned to evaluate the Serum Folate levels in patients diagnosed with lung carcinoma and to explore the association of increased serum folate levels with lung carcinoma patients.

Materials and Methods

The study was conducted in Department of Biochemistry in collaboration with the Department of Oncology, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan. Patients fulfilling the inclusion criteria were enrolled for the study.

Patients diagnosed for Lung carcinoma visiting the Outpatient Department (OPD) and In Patient Department of Department of oncology fulfilling the inclusion and exclusion criteria were enrolled for the study. Age and sex matched healthy subjects (n = 50) constituted the control group. The study was conducted after seeking approval from the Institutional Ethics Committee (IEC). Blood samples were collected by venipuncture using standard aseptic technique. Serum folate levels were estimated on VITROS 5600 Chemistry analyzer using Ortho Clinical diagnostics reagents. Results obtained were presented as mean + SD and compared statistically in the subject group and control groups.

Results

Lung carcinoma group was constituted of 50 patients diagnosed with lung carcinoma and 50 healthy individuals were enrolled as control group. Age among both the groups were comparable. When compared the serum folate levels among patients of lung carcinoma and control group it was found to be statistically significant. P value was 0.0001. (Table 1). Mean folate levels of serum folate among patients of lung carcinoma were 19.55+3.76ng/ml and in control group it was 10.86+7.97 ng/ml. Among 50 cancer patients 45 (90%) were male and 5(10%) were female. Male patients have a higher incidence and prevalence rate of lung carcinoma as compared to female.

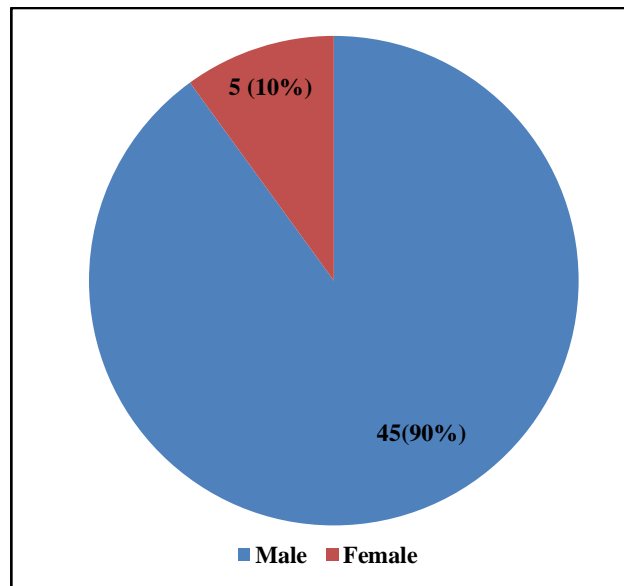


Fig 1: Distribution of cancer patients on the basis of gender

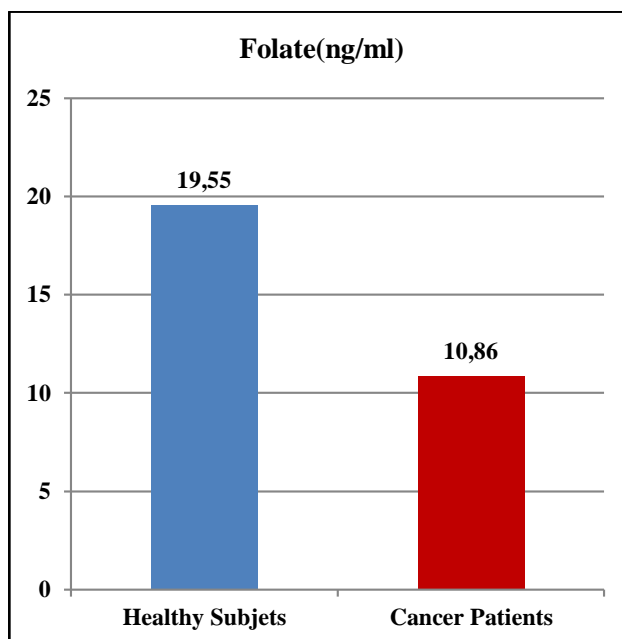


Fig 2: Comparison of Serum Folate between Cancer patients and Control group.

Table 1: Comparison of S Folate between Cancer patients and Control group

	Control (n=50)	Cancer patients (n=50)	t-value	P- value
Folate (ng/ml)	19.55+3.76	10.86+7.97	8.28	0.0001

P-value as obtained on applying student's t-test.

Discussion

Lung cancer is a principal cause of cancer-related mortality universally. Smoking being the principal cause of lung cancer. Folate aids to maintain DNA integrity and to regulate gene expression. Serum folate levels may affect the risk of several cancers, including lung cancer. In this study we evaluated the association between serum folate concentration and the lung cancer patients. In the present study Male (90%) were the more affected ones as compared to the females (10%) from lung carcinoma. Mean S. folate levels in lung carcinoma patients were 10.86+7.97 as compared to control group. Mean S. folate levels among control group was 19.55+3.76 ng/ml. Present study showed lower levels of S. Folate levels among lung cancer patients. An association of folate concentration with lung cancer risk was assessed in a number of case-control studies, but the results were varying. Various studies differed between in terms of study design (retrospective¹⁶⁻¹⁹ or prospective²⁰⁻²⁶). Some differ in data analyses methods (based on dietary questionnaires^{16,19,20,23-26} or determination of serum/plasma folate concentration.^{17,18,21,22} 2 case-control studies described significant association of higher folate intake with lower lung cancer risk was^{16,20} and 2 observational cohort studies.^{19,23} However, in other analyses²⁴⁻²⁶ relationship was not confirmed. Several studies examined an association of folate concentration with lung cancer,

but results were inconclusive. Significantly lower folate concentration was detected in cancer patients in a small retrospective study of 40 cases and 40 controls.¹⁷ However, no difference in folate concentration was found between cases and controls in another retrospective study of similar size (46 cases and 44 controls).¹⁸ In present study also lower levels of S Folate was found to be associated with lung carcinoma patients.

No significant association was seen in a nested case-control study conducted within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort between serum folate and lung cancer risk in which 300 cases and 300 controls were enrolled.²² However, it should be highlighted that in this trial participants received alpha-tocopherol or beta-carotene or placebo, so these findings could be influenced by the given supplements. A significantly lower risk of lung cancer associated with raised serum folate was reported in a large study of 899 lung cancer cases and 1815 controls from EPIC cohort.²¹ These authors observed a moderate lower risk for increasing serum folate levels, although this association was restricted to former and current smokers and was not apparent in never smokers.²¹ In meta-analysis of 4 case-control studies and 44 cases out of a cohort of 1988 participants a marginal association without significance between high serum folate levels and lower lung cancer susceptibility was reported. Exclusion of single study in the sensitivity test exerted a significant inverse relationship between serum folate levels and lung cancer risk.²⁷ The observed discrepancies in results between studies may be explained by differences in their size or design, and baseline folate concentration. Results of our retrospective study suggest that serum folate concentration is inversely associated with lung cancer diagnosis. This is consistent with the EPIC cohort, one retrospective study and meta-analysis.^{17,21,28} The mean folate concentration in our study was in controls, what is higher in comparison to that reported in all other analyses (14.4 nmol/l in EPIC²¹, 4.3 ng/ml (9.7 nmol/l) in Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study²², and 6.1 pg/ml¹⁷ and 7.8 ng/ml (17.7 nmol/l)¹⁸ in retrospective studies). It is not clear how to clarify this variation in folate concentration in particular studies/populations. In previously published analyses for determination of folate concentration were used microbiological or protein-binding methods.^{17,18,21,22} It is unlikely, but in the microbiological assay antibiotics and antifolates present in the tested sample may potentially influence grow of the bacteria, and therefore may be responsible for false results.²⁸

Conclusion

Lung cancer patients were found to have relatively low serum folate levels as compared to control group. Lower serum folate concentrations may be associated with a higher risk of lung cancer diagnosis. More studies are needed to draw a conclusion.

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