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Homocysteine Levels in Cancer Patients And its Correlation with Vitamin B_{12} And Folicacid

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Abstract
Introduction: *Homocysteine has been reported to be increased in a number of cancers includinghead and neck cancers,breast cancers,prostate cancers and colon cancers. Homocysteine is an intermediate in transmethylation reactions involving S-adenosyl methionine formed from methionine. Vitamin B12 and folic acid are required for the remethylation reaction of homocysteine. Therefor deficiency of folic acid or B12 will result in decreased methylation leading to decreased purine synthesis, formation of thymidylate and DNA methylation.An epigenetic change especially DNA methylation has been found to be associated with many cancers.Changes in methylation patterns particularly promoter specific hypermethylation and global (genome-wide)hypomethylation are thought to contribute to neoplasia and tumorgrowth.*
Methods: *Study group included twenty four newly diagnosed cases with cancer and 26 age matched controls.Serum homocysteine, vitamin B12 and folate levels were estimated.*
Results: *The study confirms the finding of higher homocysteine levels in cancer patients when compared to controls. Vitamin B12 and folate levels are significantly decreased in cancer patients.*
Conclusion: *Increase in homocysteine may be due to alteration of methionine cycle which is reported in several cancers. Altered DNA methylation may activate proto oncogenes. Decrease in folate and vitamin B12 may be due to increased demand by the rapidly dividing cancer cells.*
Keywords: *Homocysteine,vitamin B12 ,Folic acid ,DNA methylation*

I. Introduction

Homocysteine has been reported to be increased in a number of cancers including head and neck cancers,breast cancers,prostate cancers and colon cancers. There are also a number of reports that showed significant decrease in folic acid levels when homocysteine is elevated in cancers .This may be due to increased demand of folate in cancer patients and decreased daily consumption of green leafy vegetables in western countries. Decrease in folate levels have been reported for various cancers in western countries. In this study we are estimating homocysteine ,folic acid and vitamin B12 in cancer patients.

Homocysteine is a thiol containing aminoacid produced through catabolism of essential aminoacid methionine. When methionine is in excess homocysteine is degraded to cysteine through transsulfuration pathway in vitamin B6 dependent reaction.Cytseine is a precursor aminoacid for synthesis of proteins ,CoA and γ –glutamyl cysteinyl glycine (glutathione).Tissue concentrations of both homocysteine and cysteineare maintained at low levels by tight regulation. [1] Stipanuk 2004

Invitro studies have shown that homocysteine levels are positively associated with proliferation rates of cells in a variety of tumors including head and neck and breast cancers [2] as well as with oxidative damage to cells [1]. Cytseine has been considered to possess antioxidant properties through its role in glutathione synthesis the intracellular antioxidant and detoxifying agent[4]. However recent evidence from invitro and invivo studies have suggested that cysteine may act as prooxidant agent that causes DNA oxidative damage as a result of the over production of free radicals and hydrogen peroxide ,leading to gene mutation and subsequent cancer development. [1,3,5]. Elevated levels of homocysteine and cysteine are also associated with several metabolic disorders including high body mass index ,high plasma triglyceride levels ,hypertension and abnormal oxidation of low density lipoproteins which may lead to development of several cancers including breast cancer[6].

Folate,Vitamin B12 and pyridoxal 5 –phosphate,the principal active form of VitaminB6 have a number of important roles that potentially make them important in cancer. Folate is present in a number of co enzymatic forms whose main biochemical function in mammalian systems is to mediate the transfer of one carbon units at different states of oxidation. It is fundamental in the synthesis of purine and pyrimidine bases and as a methyl donor to form methyl cobalamine which is used for remethylation of homocysteine to methionine[7] .Alteration of this methionine cycle have been reported in several human malignancies[8]
Diminished levels of folate and B12 may result in misincorporation of uracil into DNA leading to chromosome breaks and disruption of DNA breaks.Folate and B12 are also involved in DNA methylation.

Methionine cycledisruptions, by reducing intracellular S –adenosyl methionine (SAM) ,can alter cytosine methylation in DNA leading to inappropriate activation of protooncogenes,repression of tumour suppressor genes and induction of malignant transformation. Alterations in DNA methylation and gene promoter hypermethylation in tumour tissues is a common event in the development of many types of cancer including head and neck squamous cell carcinoma(HNSCC) [9]

This is because neoplastic growth is frequently preceded by aberrant promoter methylation of tumour suppressor genes that promotes cell proliferation. Global hypomethylation occurs not only in transcription control regions such as promoters but also in repetitive DNA sequences such as heterochromatic regions and retrotransposons.The family of LINE 1 (long interspersed nuclear elements) retrotransposons is reportedly hypomethylated in many cancers and reflects global methylation status in the genome [10] .Thus examination of methylation at LINE 1regions has served as a proxy for measuring global methylation levels.One long interspersed nuclear elements repeat regionLRE1 located on 22q 11-q12 is a consistent indicator of global methylation status.In a large prospective study it was shown that dietary folate intake protects heavy smokers from developing lung squamous cell carcinoma[11] .

II. Aims and Objectives

1. To know the mean homocysteine levels in normal healthy individuals as well as in cancer patients in the same age group
2. To find out correlation of serum homocysteine with vitamin B12 and folate

III. Materials and methods

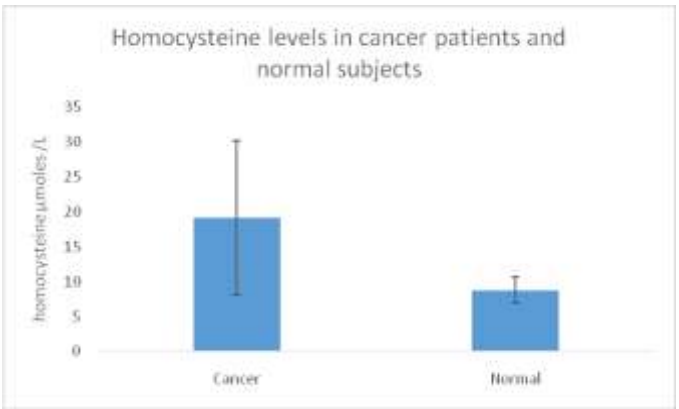
Twenty four patients of age 30 -70 years newly diagnosed cases with cancer were chosen from outpatient clinic of oncology department as cases for the study. Simultaneously twenty six apparently healthy subjects of similar age group were included as control.The study protocol complied with Helsinki declaration guidelines and was approved by the Institutional Ethics Committee .After explaining the objectives of the study to the participants written consents were obtained. Blood samples were obtained by venepuncture and were allowed to clot. Serum samples were prepared by centrifugation for five minutes at 3000 rpm. Immediately after centrifugation transfer the serum to another tube. Serum homocysteine,vitamin B12 and folate were estimated. Homocysteine levels were measured in Vitros 5,1 FS chemistry system autoanalyser[12] . Vitamin B12 levels and folate levels were estimated by immunochemistry method in Beckmann Coulter Access II and Vitros Eci immunochemistry system autoanalyser respectively[14,13].

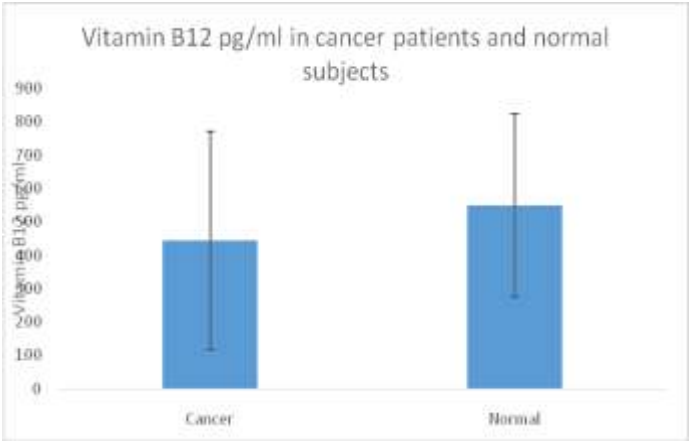
A students t test analysis was used to compare the mean values between cases and controls. Correlation of homocysteine with vitamin B12 and folic acid was also done.

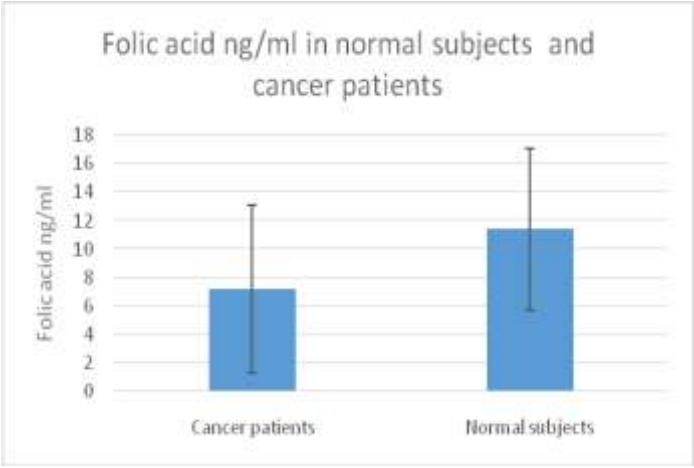
IV. Results

Results were expressed as mean ± SD. It was observed that mean homocysteine levels weresignificantly increased almost double in cancer patients when compared to control subjects. (P<0.01).Mean vitamin B12 levels were significantly lower in cancer patients when compared to controls (P<0.01).Mean folate levels were also significantly lower in cancer patients when compared to controls (P<0.001)

	Cancer	Normal	t value P value
Homocysteine	19.158 ±11.036	8.8 ±1.812	2.667
Vitamin B12	444.167 ± 325.793	549 ±273.5	1.731
Folic acid	7.187±5.959	11.38±5.69	2.7

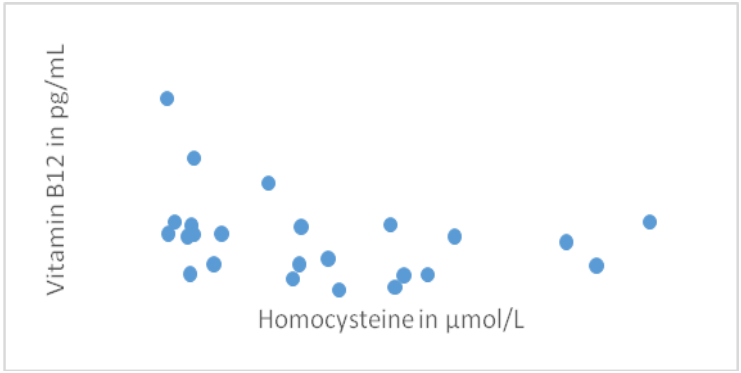






Correlation between Vitamin B12 and variable homocysteine level To study the relationship of vitamin B12 to homocysteine levels, individuals with cancer were grouped into two equal groups one group with relatively higher homocysteine and other group with lower homocysteine. In the high homocysteine group Vitamin B12 was found to be significantly decreased

Homocysteine Values	Vitamin B12 (Low homocysteine)	Vitamin B12 (high homocysteine)
Mean	579.5	308.83
SD	378.91	179.1
t value pvalue	2.14	



Scatter diagram of serum homocysteine and vitamin B12 (Correlation coefficient r= - 0.32)
Correlation between folate and variable homocysteine level

Folate levels ng/ml	Folate (Low homocysteine)	Folate (High homocysteine)
Mean	9.16	4.22
SD	6.94	1.31
t value	1.6	

V. Discussion

Homocysteine values were reported to be increased in some cancers like head and neck cancers ,prostate cancers and colon cancer. In some of these cancers folate levels were reported to be decreased. The major source of folate is green leafy vegetables.Consumption of green leafy vegetables may be less in western countries [8]. But consumption of green leafy vegetables may be adequate in Indian population, especially in vegetarians. Therefore, it is important to find out whether folate levels are high in cancer patients in India and what may be the level of vitamin B12 in cancer patients.

It was observed in our study that mean homocysteine value was almost double in cancer patients .The reference interval of homocysteine with the method that was used by this laboratory was 4.7 -12.6 µmol/L (female) and 6.6 -14.8 µmol/L (males).In our study it was observed that the folate levels was significantly decreased in cancer patients.Both vitamin B12 and folate are required for transmethylation of homocysteine to methionine. The major sources of vitamin B12 are fish and liver.Vitamin B12 levels were not reported to be significantly decreased in cancer patients in western countries. Vitamin B12 is required for dividing cells. Folate levels may also be decreased due to increased demand for folate in cancer patients due to increased cell division. It was observed that there is a negative correlation between serum homocysteine and vitamin B12 levels.As homocysteine levels increase serum B12 levels were found to decrease.vitamin B12 and folic acid are required for one carbon metabolism involving s adenosyl methionine.One carbon transfer from Sadomet was found to be an important factor in some of the epigenetic regulatory functions such as DNA methylation.Altered DNA methylation may also be a factor in some of the conditions of gene expression,especially involving proto-oncogenes.If this is so vitamin B12 and folic acid deficiency may predispose to cancer.It may also be possible that there may be other predisposing conditions of cancer in these individuals and B12 and folate deficiency may add to those conditions [15] .

VI. Conclusion

Homocysteine was significantly increased in cancers and vitamin B12 cancers.Altered DNA methylation may activate proto oncogenes. Decrease in folate and vitamin B12 may be and folate levels were significantly decreased.: Increase in homocysteine may be due to alteration of methionine cycle which is reported in several due to increased demand by the rapidly dividing cancer cells.

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