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Relevance of Serum Vitamin C Levels in Cancer Patients Undergoing Radiotherapy Treatment

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Abstract

Cancer incidence is on rise and termed as life style disease. Food and nutrients play a great role in carcinogenesis and prognosis of cancer to treatment. Recently a huge interest in role of vitamins in cancer prevention, treatment and prognosis has renewed the interest in this field.

In present study, we have studies serum vitamin C levels in cancer of head and neck, cervix and breast. Serum vitamin C levels were measured in the study group of patients undergoing radiotherapy at various intervals such as before start of radiotherapy, midway of radiotherapy, completion of radiotherapy and subsequent monthly follow-up to 6 months. For comparing vitamin C levels of cancer patient (study group), serum vitamin C levels in 50 healthy volunteers (control group) was measured.

We observed that in all the cancer patients in study group, the serum vitamin C levels were statistically significantly lower as compared to healthy volunteers and the vitamin C levels increased as the radiotherapy progressed. We further observed a correlation of vitamin C levels and the stage of the disease.

Keywords: Serum vitamin C levels; Radiotherapy; Cancer cervix; Cancer breast

Introduction

According WHO [1] report in India the Non-communicable Diseases (NCDs) account for 63% of all deaths and among them cancer is one of the major cause accounting for 9% of the deaths. Further the incidence of cancer is increasing and as per GLOBOCAN report [2] over 18 million new cancer patients and over 9 million deaths are estimated per year globally, it is second major cause of death. In India as per NCCP 2020 report [3] it is projected that 1.4 million new cancer patients and around 0.7 million deaths in a year 2020. The authors further reported that the common 5 leading cancer sites are breast, lung, mouth, cervix uteri, and tongue and the trends in cancer incidence rate showed an increase in all sites of cancer in both sexes.

Cancer is multi-factorial disease and life style including food, nutrients is one of the major cancer-causing factors. Recently there is surge of publications on food, nutrients and vitamins related to cancer incidences and prognosis [4-6]. Vitamins are essential nutrients for human metabolism and play an important role as coenzymes or enzymes in many vital processes for the normal functioning of the body. In recent years, it has become apparent that vitamins are crucial in health and human disease and several studies have shown strong relationship between vitamin levels and diseases [7-9]. Currently, it is known that vitamins can have an important role in the prevention and treatment of cancer, but until now no conclusive results were obtained. There are many studies which tried to investigate the serum vitamin C levels and also supplementary vitamin C for treating cancer however the effect of ascorbic acid on cancer has been a subject of great controversy. Padayatty S and Levine [10] has reported an extensive review on importance of vitamin C in various human ailment and reported that vitamin C regulates a variety of fundamental biological processes leading varies human diseases including cancer. In India cancer head and neck in male and cancer cervix and breast in female are the major cancers and radiotherapy is major modality of treatment for head and neck and cervix cancer [3].

Material and Methods

The present study is carried out to access the serum vitamin C levels in 90 cancer head and neck, 75 cancer cervix and 30 cancer breast patients undergoing radiotherapy treatment. All these

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cancer patients are histopathologically confirmed for malignancy and sub classified in poorly differentiated, undifferentiated and moderately differentiated carcinoma. Head and neck cancer patients were classified according to UICC TNM staging and cancer-cervix are staged according to FIGO classification [11,12].

In present study, we estimated the serum vitamin C levels in all patients undergoing radiotherapy and included in this study. For serum vitamin C level, venous blood of all the patients included in the study was taken at 9 regular intervals and serum vitamin C levels were estimated at various intervals such as before start of radiotherapy, mid of therapy, after completion of therapy, and subsequent monthly follow-up (up to 6 months). The estimation of vitamin C was done by spectrophotometric method using dinitrophenylhydrazine [13]. The data was analyzed statically for comparison of vitamin C levels at various stages of radiotherapy treatment and follow up. For comparing the vitamin C levels in cancer patients we have included a control group. The control group consisted of 50 close family members of the patient having no sign, symptoms of cancer and also not on the vitamin C supplement. We have chosen the close family member (control group) of the cancer patients (study group) so that the biases in food intake, environmental factors are not significantly different. Further the control group included only female for the cancer cervix and breast cancer patient so as avoid gender biases. The blood sample was collected for estimation of vitamin-C levels in these control group individuals once.

Results

In the present study, it was observed that the vitamin C levels in control group of individuals were 0.91 mg/100 ml ± 0.19 mg/100 ml (included male and female family members of head and neck cancer patients) and 0.79 mg/100 ml ± 0.29 mg/100 ml (included only female family members of cancer cervix and cancer breast patients). Similarly, the serum vitamin C levels in cancer head and neck patients before start of radiotherapy were 0.38 mg/100 ml ± 0.14 mg/100 ml whereas the level were 0.39 mg/100 ml ± 0.16 mg/100 ml and 0.40 mg/100 ml ± 0.17 mg/100 ml in cancer cervix and cancer breast patients respectively. It is evident from the result that in all the cancer patients of head and neck, cancer cervix and breast, the serum vitamin C levels were much lower than the control group and is statically significant. The results of vitamin C levels before start of radiotherapy (BT), midway between radiotherapy (MT) and at the completion of radiotherapy (CT), subsequent monthly follow-up up to six months (1M to 6M) are tabulated in Table 1 for head and neck cancers, Table 2 for cancer cervix and Table 3 for cancer breast. It is observed that the serum vitamin C levels during the radiotherapy treatment were found to be increasing slowly and steadily. It was further observed that during the subsequent monthly follow up of 6 months, the levels of serum vitamin C increase were statically significant in patients having good/complete response to radiotherapy treatment. We also analyzed from the study data of patient's the serum vitamin C level and stage of disease for cancer cervix are tabulated in Table 4. It was observed that as the stage of the diseases increases the vitamin C levels increase at 6 months follow up after the treatment were much lower as compared to respective control. Further analysis was done based on pathology of the cancer and observed that the well differentiated squamous cell carcinoma; the levels of vitamin C were lower than the moderately differentiated and poorly differentiated squamous cell carcinoma in head and neck cancer patients and tabulated Table 5. The vitamin C levels before the treatment and at completion of treatment compared with control for all three malignancies of Head and neck, cervix and breast are tabulated in Table 6. Based on the serum vitamin C levels estimations in the present study, it is evident that serum vitamin C levels were significantly lower before start of radiotherapy in all the patients of cancer head and neck, cervix and breast. The study results shows that the serum-vitamin C levels increases as radiotherapy progress and subsequent follow up which is statically significant and is graphically depicted in Figure 1, 2 and 3 for cancers head and neck, cervix and breast and Figure 4 shows comparison of serum vitamin C levels compared with control. The vitamin C levels and the pathology of tumor for head and neck and stage of disease in cervix are graphically shown in Figure 5, 6.

Table 1: Statistical analysis of serum vitamin C (mg/100 ml) in head & neck malignancy (n=90).

	Control	BT	MT	CT	1M	2M	3M	4M	5M	6M
Mean	0.91	0.38	0.45	0.54	0.5	0.53	0.56	0.62	0.67	0.72
SD	0.19	0.14	0.12	0.18	0.16	0.16	0.15	0.15	0.14	0.16
t		14.97	14.7	8.9	10.65	9.76	9.09	7.48	6.13	4.27
p		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

* BT: Before start of Radiotherapy; MT: Mid way of Radiotherapy; CT: At Completion of Radiotherapy; 1M: One Month follow up; 2M: Two Months follow up; 3M: Three Months follow up; 4M: Four Months follow up; 5M: Five Months follow up; 6M: Six Months follow up

Table 2: Statistical analysis of serum vitamin C (mg/100 ml) in cervix uterus malignancy (n=75).

	Control	BT	MT	CT	1M	2M	3M	4M	5M	6M
Mean	0.79	0.39	0.42	0.51	0.55	0.55	0.58	0.53	0.54	0.6
SD	0.29	0.16	0.1	0.15	0.17	0.15	0.16	0.13	0.14	0.18
t		6.66	6.84	4.76	3.98	4.03	3.35	3.86	3.35	2.45
p		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.01

Table 3: Statistical analysis of serum vitamin C (mg/100 ml) in breast malignancy (n=30).

	Control	BT	MT	CT	1M	2M	3M	4M	5M	6M
Mean	0.79	0.4	0.46	0.49	0.48	0.48	0.5	0.53	0.52	0.6
SD	0.29	0.17	0.15	0.1	0.12	0.17	0.16	0.17	0.14	0.2
t		5.92	5.24	5.07	5.15	4.72	4.57	3.8	3.77	2.2
p		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	NS

Table 4: Comparison of vitamin 'C' level in cervix uterus malignancy according to stage of disease.

	BT			6 months follow up		
	II A	II B	III	II A	II B	III
Mean	0.4	0.39	0.39	0.77	0.61	0.53
SD	0.15	0.21	0.15	0.19	0.23	0.24
t				3.49	1.72	2.24
p				<0.005	NS	NS
% (↑/↓)				48.1↑	36.1↑	26.5↑

II A- STAGE II A Disease
II B- STAGE II B Disease
III- STAGE III Disease

Table 5: Comparison of vitamin 'C' level (mg/100 ml) in head and neck malignancy according to histopathological grading.

	BT			6 months follow up		
	Well	Mod	Poorly	Well	Mod	Poorly
Mean	0.34	0.38	0.41	0.71	0.71	0.77
SD	0.14	0.14	0.13	0.14	0.17	0.18
t				7.32	8.55	5.7
p				<0.001	<0.001	<0.001
% (↑/↓)				52.2↑	46.5↑	46.8↑

- BT- Before radiotherapy
- Well- Well differentiated squamous cell carcinoma
- Mod- Moderately differentiated squamous cell carcinoma
- Poorly- poorly differentiated squamous cell carcinoma
- % (↑/↓)- Percentage of increase/decrease in vitamin C levels at 6 months follow up compared with before therapy levels

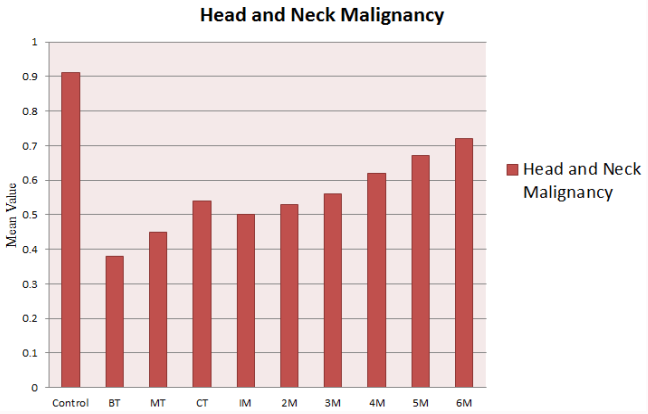

Figure 1: Comparison of serum vitamin C levels in cancer head & neck patients.
* Vitamin C levels in mg/100 ml on Y axis and interval of estimation on X axis

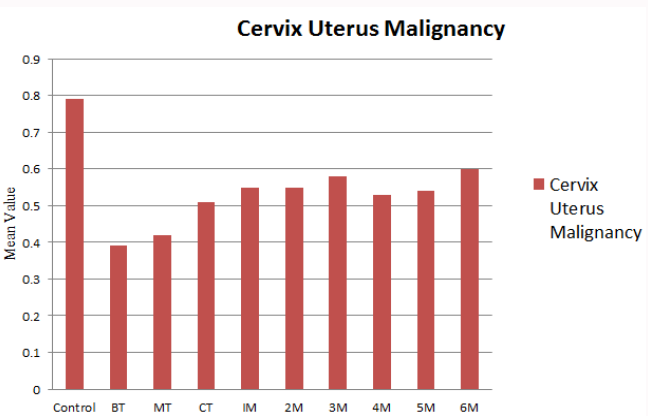

Figure 2: Comparison of serum vitamin C levels in cancer cervix patients.
* Vitamin C levels in mg/100 ml on Y axis and interval of estimation on X axis

Discussion

Interest in food and nutrients related to various human elements including serum-vitamin C levels has been reported by various authors [14]. Vitamin C levels, supplementation of vitamin C and the cancer tumor growth rate have also been studied extensively and reported [8]. However, only few studies are found in literature by authors related to radiotherapy treatment and subsequent of vitamin C level variations.

Study by Srivastava et al. [15], evaluated vitamin-A, E, C levels in 97 histopathologically confirmed cancer cervix patients undergoing radiotherapy treatment. The objective of their study was to analyze the level of serum Vitamin A, E and C at different phases of concurrent chemo-radiotherapy (before, during, immediately after, and at three months follow up) in carcinoma cervix patients with healthy controls and their association with treatment response was investigated. They have estimated vitamin A, E and C levels before start of radiotherapy, midway, completion of radiotherapy, and at 3 months follow-up. They estimated the vitamin A, E and C levels in 30 age matched healthy control group. They found that the vitamin A, E and C levels were lower than the control group and the values start increasing as radiotherapy progresses with approaching to control group levels at 3 months follow up. They further commented that the lower serum vitamin A, E, and C levels before treatment could be a cause or an effect of cancer. They observed that in cancer cervix patients, before the start of radiotherapy, the vitamin C levels were lower than the age matched healthy volunteers. Further they observed that the levels of vitamin C increases as radiotherapy progresses. There are confusing studies reported on injecting intravenously vitamin C and as food ingredients orally. Many studies report that it is impracticable to intravenously supplement vitamin C more over the outcome did not reach to any conclusion [16].

Bhuvarahamurthy et al. [17] reported a study in uterine cervical carcinoma patients (before and after radiotherapy and radiotherapy combined chemotherapy) and compared with controls and observed that some of the antioxidant components such as vitamin E and C are reduced in cervical cancer. They found the reduced levels of vitamin E and C were normalized after treatment, which is correlated with treatment efficacy. The present study results substantiate the findings of the earlier reports.

Table 6: Comparison of serum vitamin C (mg/100 ml) levels of study group with control group.

	Before Radiotherapy (BT)		Completion of Radiotherapy (CT)		Control
	mean	Percentage variation compared with control	mean	Percentage variation compared with control	
Head & Neck	0.38	58.3%↓	0.54	40.7%↓	0.91
Breast	0.4	49.4%↓	0.49	38%↓	0.79
Cervix	0.39	50.7%↓	0.51	35.5%↓	

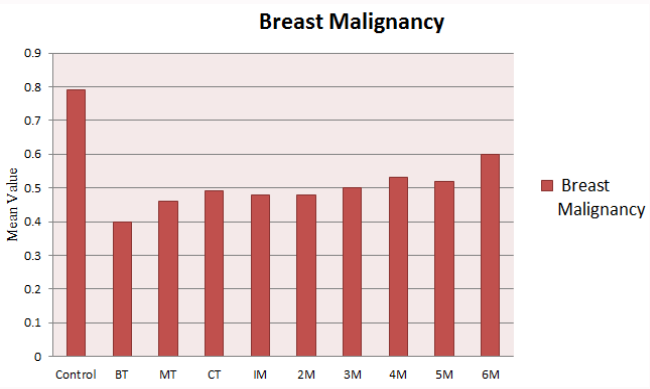

Figure 3: Comparison of serum vitamin C levels in cancer breast patients.
* Vitamin C levels in mg/100 ml on Y axis and interval of estimation on X axis

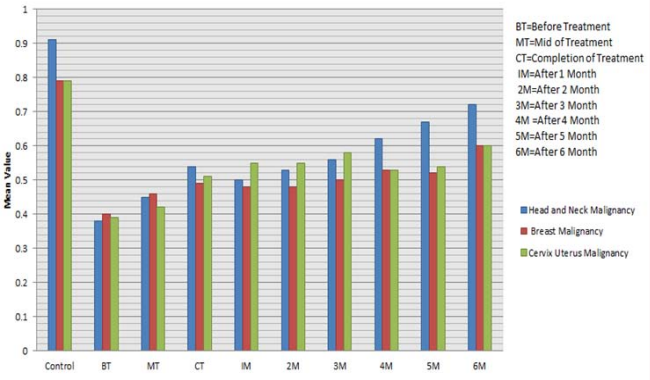

Figure 4: Comparison of serum vitamin C levels in cancer head and neck, Cervix and breast patients.
* Vitamin C levels in mg /100 ml on Y axis and interval of estimation on X axis

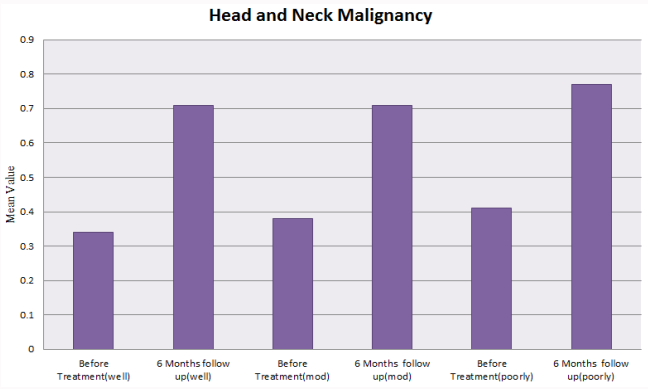

Figure 5: Serum Vitamin C levels (mg/100 ml) in well differentiated, moderately differentiated and poorly differentiated squamous cell carcinoma of head and neck patients before start of radiotherapy and at 6 months follow up.

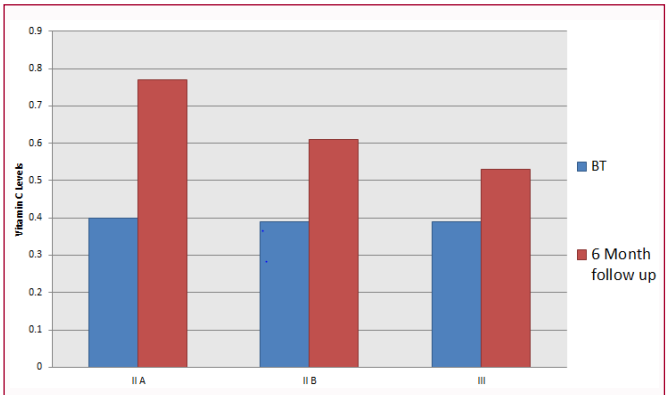

Figure 6: Comparison of vitamin 'C' level in cervix uterus malignancy according to stage of disease before treatment and 6 months follow up.

Another study by Aune et al. [18], found a significant inverse association between blood concentrations of total carotenoids, b-carotene, a-carotene, and lutein and breast cancer risk. Authors [19] have reported a study on vitamin E levels in 33 cancer cervix patients undergoing radiotherapy treatment. They have measured the serum vitamin E levels before start of radiotherapy, midway of radiotherapy completion of radiotherapy and monthly follow up to 6 months. They observed decreased levels of vitamin E in all the cancer cervix patients included in the study as compared to age matched healthy volunteers. Further they reported the increasing levels of vitamin E as therapy progresses and a correlation of vitamin E with stage of disease.

Publications by Grosso et al. [20] discusses possible mechanisms of anti-cancer action, vitamin C has been hypothesized to counteract inflammation and subsequent oxidative damage to DNA, which play a role in the initiation and progression of cancer. Vitamin C may also function as cancer cells killer, due to its pro-oxidant capacity, although the killing of cancer cells is dependent on extracellular H_2O_2 formation with the ascorbate radical as an intermediate. Moreover, vitamin C may increase collagen synthesis and inhibit hyaluronidase and, in this way, it may prevent cancer spread by increasing extracellular matrix, thus creating walling in tumors [21].

Hoffman [22] have studied micronutrient requirements of cancer patients and reported that cancer patients show low levels of vitamin, and suggested administration of vitamin C can improve the immune system.

Huijskens et al. [23] have reported a study on serum ascorbic acid levels in patients with hematological malignancies. They have measured serum ascorbic acid levels in 42 non-selected hemato-oncology patients and found that all these cancer patients, the serum ascorbic acid levels were very low (statically significant) as compared to levels in 72 healthy volunteers. Mayland [24] have reported that vitamin C deficiency is common in patients with advanced cancer based on their study of 50 patients of advanced cancers in which serum vitamin C levels were measured before start of cancer treatment. Further they observed that patients with low plasma concentrations of vitamin C have a shorter survival.

Conclusion

The present study concludes that vitamin C levels are altered in cancer patients and the levels vary with the treatment and progression of the disease.

Highlights

- Cancer is life style disease
- Nutrition and vitamins have a role in cancer development, prognosis and diagnosis
- Vitamin C levels in cancer patients are lower than the healthy volunteers
- Vitamin C levels start increasing as the tumour starts

regressing in response to treatment

Declaration

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by (Arun Chougule), (Mary Joan) and (Bhawani Kochar). The first draft of the manuscript was written by (Arun Chougule) and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data transparency

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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