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Serum vitamin A, E and C status in cervical cancer patients undergoing Concurrent Chemo-Radiotherapy, an institutional study

Anju Shrivastava[a], Satyajit Pradhan[b], Surendra Pratap Mishra[c], Anupam Kumar Asthana[a], Sunil Choudhary[a], Kulsoom Zahra[c], Lalit Mohan Aggarwal[a,*]

[a] Radiotherapy and Radiation Medicine, Banaras Hindu University, Institute of Medical Sciences, Varanasi, 221005, Uttar Pradesh, India
[b] Mahamana Pandit Madan Mohan Malviya Cancer Centre, BHU Campus, Varanasi, 221005, India
[c] Biochemistry, Banaras Hindu University, Institute of Medical Sciences, Varanasi, 221005, Uttar Pradesh, India

HIGHLIGHTS

- Vitamin A, C, and E levels lowered in all stages of cervical carcinoma compared to healthy controls.
- These vitamin levels were consistently decreased during concurrent chemoradiotherapy and immediately after therapy.
- All the alteration are trending towards normal value at the time of 3 months follow up.

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ABSTRACT

Vitamin A, E, and C are powerful non enzymatic antioxidants responsible for capturing free radicals, and thus, they prevent oxidative chain reactions. Persistent oxidative stress may cause resistance to apoptosis, which promotes cell proliferation and leads to the tumor and its angiogenesis. Serum level of Vitamin A, E, and C were estimated in carcinoma cervix patients at different phases of treatment and compared it with healthy controls. Ninety-seven histopathologically diagnosed Cervical Carcinoma patients, and thirty age-matched healthy controls were included in this study. Blood samples were taken once from the controls. From each patient undergoing Radiotherapy, four samples were collected i.e., before, during, immediately after and at three months follow-up of treatment. The serum was separated and stored at −20 °C until examination. Statistical analysis was done with the commercial SPSS 21.0 package for Windows (SPSS, IBM Bangalore). P-value < 0.05 was considered statistically significant. Vitamin A, E, and C levels were lower in carcinoma cervix patients of all FIGO (International Federation of Gynecology and Obstetrics) stages compared to controls. Patient serum levels of vitamins decreased again during Concurrent Chemo-Radiotherapy and immediately after the therapy. There is an elevation shown by these vitamins after three months of follow up. The results indicate that the lower serum vitamin A, E, and C levels before treatment could be a cause or an effect of cancer. Further decrease in vitamin levels during and immediately after therapy shows the high oxidative stress during the treatment period, which is beneficial for the patient. These altered vitamin levels were normalized during the time of follow-up.

1. Introduction

According to the National Institute of Cancer Prevention and Research (NICPR) In- dia, Cervical Cancer is the 3rd most common cancer in the country. In India, around 96,922 women are newly diagnosed and 60,078 women die of cervical cancer every year as per Globocan 2018 [1]. The prevalence of cervical cancer is higher in rural areas as compared to cities. It significantly rises around the age of 45 years and peaks at 55 years [2]. In addition to Human Papillomavirus infection, co-factors such as parity, early age of marriage, genital hygiene, promiscuity, use of oral contraceptives, smoking, tobacco, alcohol, immune suppression, and poor nutrition have been associated with the development of cervical cancer [3,4].

All the factors mentioned above lead to oxidative stress and are responsible for producing free radicals in the body [5]. Persistent oxidative stress may cause resistance to apoptosis, which promotes cell

* Corresponding author.
E-mail addresses: anju.joyshrivastav@gmail.com (A. Shrivastava), satyajit.pr@gmail.com (S. Pradhan), drsurendram2@gmail.com (S.P. Mishra), npmasthana@yahoo.com (A.K. Asthana), drsunil104@gmail.com (S. Choudhary), kulsoom.zahra19@gmail.com (K. Zahra), lalitm@bhu.ac.in (L.M. Aggarwal).

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proliferation in vitro and leads to the tumor and its angiogenesis [6]. Inherent oxidative stress may affect several functions in cancer cells such as cell proliferation, promotion of mutations, genetic instability, alterations in cellular sensitivity to anticancer agents, invasion, and metastasis [7]. The extent of Reactive Oxygen Species (ROS) induced oxidative damage can be decreased by the efficiency of antioxidant defense mechanisms. Antioxidants are molecules present in a low concentration which inhibit or quench free radical reactions and delay or inhibit cellular damage. In this, non-enzymatic antioxidants or dietary antioxidants (Vitamin A, E & C) plays an influential role by interrupting free radical chain reactions [8].

Vitamin A (Retinol) has a potent antioxidant effect by quenching singlet oxygen. It helps in cell division and differentiation, regulates Immune System, prevents the appearance or impedes the development of cancerous cells, also provides anti-mutagenic, anti-tumoral, immunostimulant, antiulcer and degenerative properties on the human [9]. Vitamin E (α-tocopherol) exert antioxidant effects by bindings to the free radicals and neutralizing its unpaired electron, it scavenges lipid peroxyl radicals in vivo as well as in vitro systems and also aids the process of wound healing [10]. Vitamin C (ascorbic acid) acts as a chain-breaking antioxidant, a reducing agent, or an electron donor. It scavenges free radicals and inhibits lipid peroxidation. It also promotes the regeneration of α-tocopherol. The deficiency of vitamin C may cause infections [10].

Radiotherapy is the main line of treatment for cervical cancer, which is usually a combination of external beam pelvic radiation and intracavitary brachytherapy. Combinational approaches have been tried to increase the therapeutic response. One such procedure is concomitant chemo-radiation (Radiation therapy + Weekly Cisplatin). Chemotherapy and radiation have a synergistic or additive effect and interact with spatial cooperation — radiation focusing on the local disease. Chemotherapy concentrates on shrinkage of macroscopic disease and at controlling micro-metastases in the course of the disease [11]. The inclusion of concurrent chemotherapy reduces metastasis and improves survival. The effects of radiation and anticancer drugs are mediated by the production of free radicals, which act on DNA to produce lethal cell damage [12,13].

Studies have addressed the impact of radiotherapy on Vitamin levels in patients with different stages of cervical cancer are less in number. The results of a hospital-based, case-control study of cervical cancer recommend that a diet high in fruits, vegetables, dietary fibers, vitamin C, E, A, α-carotene, β-carotene, folate, lutein, and lycopene may perform a vital role in overcoming the risk of cervical cancer independent of non dietary risk factors [8].

Another study in uterine cervical carcinoma patients (before and after radiotherapy and radiotherapy combined chemotherapy) and compared with controls, some of the antioxidant components such as vitamin E and C are reduced in cervical cancer. The reduced levels of vitamin E and C were normalized after treatment, which is correlated with treatment efficacy [14]. The objective of this study is to analyze the level of serum Vitamin A, E and C at different phases of concurrent chemoradiotherapy (before, during, immediately after, and at three months follow up) in carcinoma cervix patients with healthy controls and their association with treatment response were investigated.

2. Materials and method

2.1. Ethical statement

The study was accepted by the ethical committee of the Institute of Medical Sciences, Banaras Hindu University (ECR/Bhu/Inst/UP/2013/Re-registration-2017 dt.January 31, 2017), with the Ethical Code Dean/2018/EC/329 on the date January 02, 2018. Informed written con-sent from all participants was obtained.

2.2. Subjects

This study was carried out in the Department of Radiotherapy and Radiation Medicine, Sir Sunderlal Hospital, with the collaboration of the Department of Biochemistry, Institute of Medical Sciences, Banaras Hindu University Varanasi between January 2018 to March 2019. Ninety-seven histologically proven cervical cancer patients referred to the Department of Radiotherapy and Radiation Medicine, were enrolled in the study. The clinical staging was done by an oncologist and classified according to the International Federation of Gynecology and Obstetrics (FIGO) staging of cancer cervix [15].

Thirty otherwise healthy, age-matched females, of the same socioeconomic background, came as bystanders of the patient were recruited as controls, with proper written consent. The exclusion criteria were pregnancy at the time of sampling, chronic diseases like diabetes, liver disease or autoimmune disorders, acute infections at the time of sampling, an immuno-compromised state, history or laboratory evidence of malignancy and not being under any pharmacological therapy.

2.3. Treatment regimen

In concurrent chemoradiotherapy (CCRT), all patients were treated with External Beam Radiotherapy (EBRT), five fractions weekly, of 2 Gy (Gy) per fraction were delivered for five weeks. A total dose of 46–50 Gy was administered. Concurrent cisplatin was given weekly at a dose of 40mg/m2. Within one week after completion of EBRT, the patient received High Dose Rate (HDR) Intracavitary Brachytherapy with an iridium-192 source. A total dose of 18–21 Gy with 7 Gy–9 Gy per insertion once per week in 2–3 fractions. The overall treatment time was 41–57 days [11].

2.4. Blood sampling and processing

Under aseptic precautions, 5 ml of the random venous blood sample was drawn from cervical cancer patients as well as controls. Clean and dry disposable tubes were used to collect the blood. It was left to stand for 30 min at room temperature for the retraction of the clot. Then centrifuged at 3000 rpm for 10 min to separate the serum. The serum samples were stored at −20 °C in the refrigerator for further analysis.

From all patients with cervical cancer, four blood samples were collected at different phases of the treatment: Phase 1, before the start of therapy; Phase 2, during the course of concurrent chemoradiotherapy, i.e after 13 fraction of EBRT; Phase 3, immediately after the completion of brachytherapy and Phase 4, after 3 months of follow-up. A single blood sample was taken from the controls.

2.5. Biochemical estimations

The vitamin A in the serum of the patients and controls was measured by using the technique described in Paterson and Wiggins [16]. Spectrophotometric method utilizing the destruction of vitamin A by ultraviolet (UV) irradiation has been employed for the determination of the sample 'vitamin A' level. Retinol has an absorption peak at 327 Nanometer (nm) and can be determined by reading the absorbance at this wavelength before and after irradiating with ultraviolet light to destroy the retinol present.

The vitamin E was tested using the method described in Quaife et al. [17]; based on the Emmerich–Engel reaction, i.e., reduction by tocopherols of ferric to ferrous ions forms a red complex with α, α-dipyridyl.

The vitamin C level in the serum was examined using the method reported by McMurray and Gowenlock [18]. It involves oxidation of vitamin C by copper followed by treatment with 2,4-Dinitrophenyl hydrazine (DNPH). Dehydroascorbic acid coupled with DNPH and when treated with sulphuric acid forms an orange colour compound which was measured at 520 nm.

All the chemicals utilized in this study were of the scientific-grade purchased from Sigma Chemical Co. (St. Louis, MO, USA) and Merck (Darmstadt, Germany).

Samples were run in duplicate, mean values of the readings were considered for final results. We had performed the experiments using single protocol mentioned in material and method section.

Normal Values of Serum Vitamin A, E, and C.

Vitamin A (serum) 30–95 μg/dL.

Vitamin E (serum) 550–1700 μg/dL.

Vitamin C (serum) 600–2000 μg/dL.

2.6. Statistical analysis

Statistical analysis was conducted with the commercial SPSS 21.0 package for Windows (SPSS, IBM Bangalore). All values were expressed as ± the mean Standard Deviation (SD). Statistical significance was assessed by using Independent T-Test (within the group comparison). One-way ANOVA was performed for multiple comparisons between the groups. A p-value < 0.05 was considered statistically significant.

3. Results

During the period from January 2018 to March 2019, there were 97 patients, and 30 controls found eligible for the study. The median age of patients was 52.6 ± 4 7.2 years, and control subjects were 50.27 ± 7.8 years ranging from 35 to 70 years old. The majority of patients had squamous cell carcinoma, and others with adenocarcinoma. The FIGO stage ranged from I to IV. Nineteen FIGO Stage I, Fortytwo FIGO stage II, Twentynine FIGO stage III, and Seven FIGO stage IV patients, respectively.

The levels of serum antioxidants such as vitamin A, vitamin E, and vitamin C in different FIGO stages (I, II, III, IV) of uterine cervical carcinoma before, during, after radiotherapy combined chemotherapy and three months follow up with age-matched controls are shown in Fig. 1.

In Table 1 we considered all stages of cases (N = 97) as a single group in all phases of the treatment i.e, before, during, immediately after, and three months follow up. It is then compared with control (N = 30) using an Independent T-test. The results were highly significant ($p < 0.001$) and shows an overall pattern that the vitamin (A, C, & E) levels were lowered in patients of all stages of cervical carcinoma. It was again continuously decreasing during the time of concurrent chemoradiotherapy and immediately after the therapy. The patients show an elevation in vitamin (A, C,& E) levels at the time of follow up which trending towards the normal.

According to Table 2, when compared to control, vitamin A was significantly decreased ($P < 0.001$) in carcinoma cervix patients of all the four stages. Vitamin A level in the serum was comparatively low compared to vitamin E and C. It was found to be unaltered in uterine cervical carcinoma Stage I before and during concurrent chemoradiotherapy but the level lowered immediately after the completion of brachytherapy, and shows a hike after three months of follow up. In FIGO stage II, III & IV Vitamin A values are significantly decreasing ($P < 0.001$) before, during, and after therapy and shows an elevation during the time of follow up.

The levels of vitamin E were found to be significantly ($P < 0.001$) low before treatment in all FIGO stages as compared to the control group. As the treatment progresses, the vitamin E level decreases significantly till the end of the treatment. All the groups also showed an elevation in their vitamin E levels during the time of follow up.

Compared with the control Vitamin C levels are significantly ($P < 0.001$) lowered in all stages of carcinoma cervix. In all four stages of carcinoma cervix, there is again a significant decline in vitamin C levels during and immediately after the treatment. The level increased and approaching the control value during the time of 3 months follow up.

In reference with the normal values, overall vitamin A levels (Table 1) of controls were in normal range. Patients before treatment was on the lower limit of normal range. While during and immediately after the treatment values lowered down and at the time of follow-up values shows a trending towards the normal range.

Vitamin C levels of the controls and before treatment patients was within the normal range, but during and immediately after the treatment values of vitamin C falls below the normal range. The values shows an elevation at the time of follow up.

Vitamin E levels of the controls, before and during treatment patients was within the normal range, but immediately after the treatment values of vitamin E falls below the normal range. The values shows an elevation at the time of follow up.From Table 2 it was observed that, before treatment values of vitamin A, C, and E were dropped below the normal levels in the advanced stages of carcinoma cervix.

Out of these 97 patients, all the patients had complete response, except for four patients show distant metastasis at the time of 3 months

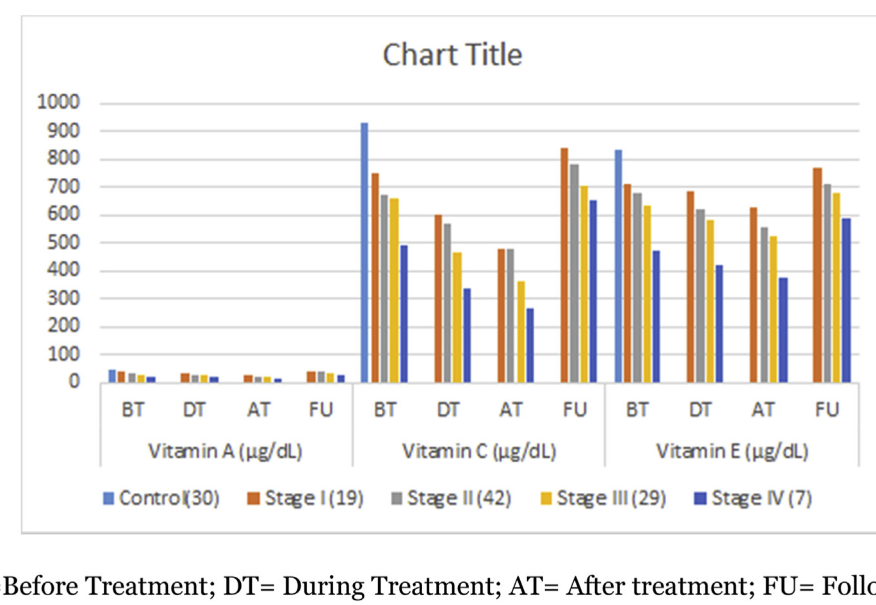

Fig. 1. Level of serum Vitamin A, Vitamin C, and Vitamin E data in μg/dL of control (N = 30) and Carcinoma cervix patients; N = 97 (Stage I-19; Stage II-42; Stage III-29 and Stage IV-7) under-going Concurrent chemoradiotherapy.

Table 1
Overall level of serum Vitamin A, Vitamin C, and Vitamin E data in μg/dL in control (N = 30)and Carcinoma cervix patients (N = 97) Before, During, Immediately after, and 3 Months Follow up of Concurrent chemo radiotherapy.

Variable	Mode of therapy Concurrent Chemo Radiotherapy	Cases (N = 97) mean ± SD	Control (N = 30) mean ± SD	P-value
Vitamin A (μg/dL)	Before	30.88 ± 4.64	44.82 ± 10.01	< 0.001
	During	28.41 ± 5.08		< 0.001
	Immediately After	21.78 ± 3.36		< 0.001
	3 Months Follow up	37.89 ± 3.48		< 0.001
Vitamin C (μg/dL)	Before	671.35 ± 62.41	932.66 ± 52.42	< 0.001
	During	527.28 ± 80.59		< 0.001
	Immediately After	429.65 ± 75.59		< 0.001
	3 Months Follow up	760.93 ± 69.16		< 0.001
Vitamin E (μg/dL)	Before	658.30 ± 59.72	832.73 ± 85.51	< 0.001
	During	608.83 ± 64.06		< 0.001
	Immediately After	548.27 ± 62.12		< 0.001
	3 Months Follow up	705.08 ± 46.97		< 0.001

Table 2
Level of serum Vitamin A, Vitamin C, Vitamin E data in (μg/dL) of control (N = 30) and Carcinoma cervix patients (FIGO I, II,III, IV)Before, During, Immediately after, And 3 Months Follow up of Concurrent chemo radiotherapy.

Groups	N = 127	Mode of therapy Concurrent Chemo Radiotherapy	Vitamin A (μg/dL) mean ± SD	Vitamin C (μg/dL) mean ± SD	Vitamin E (μg/dL) mean ± SD
Control	30		44.82 ± 10.01	932.66 ± 52.42	832.73 ± 85.51
FIGO I	19	Before	38.42 ± 1.49	747.87 ± 13.98	711.93 ± 11.70
		During	37.25 ± 0.99	600.45 ± 44.96	684.77 ± 14.24
		Immediately After	27.53 ± 1.21	477.27 ± 38.59	629.06 ± 20.25
		3 Months Follow up	41.82.40 ± 1.58	841.11 ± 64.81	770.40 ± 16.34
P-value			< 0.001	< 0.001	< 0.001
FIGOII	42	Before	31.25 ± 0.64	675.45 ± 21.75	682.30 ± 8.44
		During	28.34 ± 0.51	569.61 ± 24.63	622.81 ± 11.39
		Immediately After	21.90 ± 0.44	481.01 ± 27.19	556.79 ± 12.52
		3 Months Follow up	39.48 ± 0.78	782.04 ± 34.30	712.74 ± 9.48
P-value			< 0.001	< 0.001	< 0.001
FIGOIII	29	Before	27.71 ± 0.33	658.23 ± 16.83	632.47 ± 10.44
		During	25.31 ± 0.38	464.05 ± 15.90	583.77 ± 11.56
		Immediately After	19.16 ± 0.54	363.51 ± 26.60	524.39 ± 14.48
		3 Months Follow up	34.80 ± 1.20	703.95 ± 21.57	678.29 ± 19.24
P-value			< 0.001	< 0.001	< 0.001
FIGOIV	7	Before	21.40 ± 0.54	493.45 ± 27.75	475.75 ± 20.59
		During	18.17 ± 0.90	337.67 ± 44.07	422.60 ± 20.46
		Immediately After	16.36 ± 1.38	266.22 ± 25.56	376.81 ± 15.18
		3 Months Follow up	30.56 ± 0.94	652.74 ± 29.78	592.78 ± 7.96
P-value		< 0.001	< 0.001	< 0.001	

follow up.

4. Discussion

Vitamin A, E, and C are powerful non-enzymatic antioxidants responsible for capturing free radicals, and thus, they prevent oxidative chain reactions [19]. In this study, it was seen that there is a significant decrease in Vitamin A, E, and C levels in patients of all four FIGO stages of cervical carcinoma as compared to the controls.

Antioxidant Vitamin A, E, and C depletion in the circulation of cervical carcinoma patients before treatment can be explained in different ways; it may be a cause or an effect of cancer. It is noted that in malnourished women and women who consume fewer amounts of fruits and vegetables are associated with cervical cancer. Thus the decreased Vitamin A, E, and C observed in cervical cancer patients can also be attributed to a large extent, to the depletion of nutrition in the diet [20]. From the studies it is clear that the increased number of free radicals may play a role in the development of cancer and other health conditions [21]. So there will be a more burden on antioxidant vitamins to scavenge these extra free radicals due to cancer may cause its depletion in circulation. It may also be due to sequestration of these vitamins by tumor cells for its growth [12]. Tumor cells have been reported to seize essential antioxidants to meet the demands of the growing tumor. During tumor initiation cells undergo modifications in both genetic aberrations and the microenvironment, which can increase the levels of ROS. Excessive accumulation of ROS in the tumor cell can lead to growth arrest or death, thereby suppressing tumor progression. Cellular drivers of tumor initiation and progression have been shown to increase utilization of antioxidants to combat oxidative stress which can promote the expansion of tumors by rescuing the viability of unhealthy, stressed tumor cells [22].

Radio Therapy has been considered as a significant primary treatment approach of cervical cancer for more than half a century. From 1999, several randomized clinical trials confirmed that "compared with Radiotherapy, the addition of cisplatin-based concurrent chemotherapy could enhance the survival of cervical cancer patients" [23].

During concurrent chemoradiotherapy and immediately after brachytherapy, it is observed that there is a significant reduction in antioxidant Vitamin A, E, and C in Carcinoma Cervix patients. It can be explained by elevated levels of oxidative stress due to concurrent chemoradiotherapy or due to reduced food intake or vomiting caused by cisplatin.

The ability of ionizing radiation to destroy cells is the basis of Radiation therapy. This therapy requires the generation of ROS. In the presence of oxygen, these radicals (hydroxyl radicals, superoxide anion, and other organic radicals), increased the formation of other ROS, such as peroxides. Therefore, adverse radiation effects would be influenced by these increased radicals, affecting the cellular antioxidant status [24].

In chemotherapy, various agents induce cell death by oxidative stress either directly, leading to the disruption of redox signaling and ROS scavenging, or indirectly by reducing intracellular levels of antioxidants and deactivating the cellular defense. Cisplatin was the first heavy metal used for treating cancer, and it has been widely used to treat solid tumors of lung, ovary, testes, and lymphoma, among others. Its mechanism of action involves the generation of intense oxidative stress but also causes numerous side effects due to their toxicity [25]. Its mechanism of action unite with the expression of p53 (tumor suppressor gene), p21 protein (cell cycle regulator), anti-apoptotic Bax proteins, and the cleavage of Poly ADP-ribose Polymerase (PARP) and caspases 3 and 9 [26].

Antioxidants exert a protective effect against these free radicals. Vitamin A or retinol can combine and neutralize peroxyl radicals before they produce lipid peroxidation. Vitamin E family includes tocotrienols and tocopherols are very lipophilic molecules. They exert an antioxidant action due to their ability to join biological membranes, stabilizing and protecting them against lipid peroxidation. Vitamin C or ascorbic acid is recognized for its electron-donating ability; it inhibits the collection of oxidizing agents and free radicals. It is particularly efficient in eliminating superoxide anion radicals, hydrogen peroxide, hydroxyl, singlet oxygen, and Reactive Nitrogen Species [19].

Vitamins defend healthy cells from the side effects of ROS. The reduced vitamin levels during concurrent chemoradiotherapy and immediately after the brachytherapy indirectly shows the elevation in free radicals in the body, which indicates the efficacy of the treatment. It is well known that blood vitamins mainly depends upon dietary intake. In the current study, it has been observed that most of the patients had vomiting during cisplatin administration. Hence, it is worth mentioning that multivitamin supplementation was included in the treatment regimen to make the treatment more productive; the dose of supplement contained the recommended daily doses.

It is also noted that the supplementation of vitamins in cervical cancer patients undergoing the treatment of chemotherapy combined with radiation increased the quality of life. Most of the patients displayed lower antioxidant levels than recommended. It is observed that women who took supplements during the treatment had shown less fatigue than women who did not receive them, which is similar to other studies [26]. During follow up, the levels of serum antioxidants vitamin A, E, and C were showing a significant rise. The increase in antioxidant concentration in serum may be due to the death of tumor cells by radiation or the arrest of tumor growth by chemotherapeutic agents. The normalization of vitamins after therapy may also be due to supplementation of vitamins during treatment, increased food intake, and the absence of emesis.

Although the precise mechanisms by which oxidative stress can produce cancer are still difficult to establish, our findings suggest that decreased antioxidant vitamin levels may play a role in the etiology and progression of cervical carcinoma. Antioxidant depletion in circulation may be due to the scavenging of lipid peroxides as well as sequestration by tumor cells. Further reduction of vitamins observed in the serum during and immediately after treatment of cervical cancer patients in the present study can be attributed to the efficacy of the procedure. The normalization of vitamins during follow up support this statement. A long term study with the evaluation of both oxidative stress and antioxidants simultaneously can say things more clearly and effectively.

Author contributions

Lalit Mohan Aggarwal, Anju Shrivastava, Surendra Pratap Mishra, Satyajit Pradhan conceived, designed the study, and drafted the manuscript. Anju Shrivastava, Kulsoom Zhara performed the experiments. Sunil Choudhary, Satyajit Pradhan, Anupam Kumar Asthana, Anju Shrivastava helped in Formal analysis, conceptualization, drafting and methodology. All authors performed editing and approving the final version of this paper for submission, also participated in the finalization of the manuscript and approved the final draft.

Author statement

Lalit Mohan Aggarwal, Anju Shrivastava, Surendra Pratap Mishra, Satyajit Pradhan conceived, designed the study, and drafted the manuscript. Anju Shrivastava, Kulsoom Zahra performed the experiments. Sunil Choudhary, Satyajit Pradhan, Anupam Kumar Asthana, Anju Shrivastava helped in Formal analysis, conceptualization, drafting and methodology. All authors performed editing and approving the final version of this paper for submission, also participated in the finalization of the manuscript and approved the final draft.

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Declaration of competing interest

None.

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References

[1] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 68 (6) (2018) 394–424.

[2] Cervical Cancer | Risk Factors for Cervical Cancer | India against Cancer, (2019 Jun 21) Available from: http://cancerindia.org.in/cervical-cancer/.

[3] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2018, CA A Cancer J. Clin. 68 (1) (2018) 7–30.

[4] S.J. Chopra, A. Mathew, A. Maheshwari, N. Bhatla, S. Singh, B. Rai, et al., National cancer grid of India consensus guidelines on the management of cervical cancer, J. Glob. Oncol. 4 (2018) 1–15.

[5] S. Reuter, S.C. Gupta, M.M. Chaturvedi, B.B. Aggarwal, Oxidative stress, inflammation, and cancer: how are they linked? Free Radic. Biol. Med. 49 (11) (2010) 1603–1616.

[6] S. Ebrahimi, A. Soltani, S.I. Hashemy, Oxidative stress in cervical cancer pathogenesis and resistance to therapy, J. Cell. Biochem. 120 (5) (2019) 6868–6877.

[7] M. Nishikawa, Reactive oxygen species in tumor metastasis, Cancer Lett. 266 (1) (2008) 53–59.

[8] P. Nobosse, E.N. Fombang, C.M.F. Mbofung, The effect of steam blanching and drying method on nutrients, phytochemicals and antioxidant activity of aoringa (Moringa oleifera L .) leaves, Adv. J. Food Sci. Technol. 5 (2) (2017) 53–60.

[9] A.A. de Carvalho Melo-Cavalcante, L. da Rocha Sousa, M.V.O.B. Alencar, J.V. de Oliveira Santos, A.M. oliveira da Mata, M.F.C.J. Paz, et al., Retinol palmitate and ascorbic acid: role in oncological prevention and therapy, Biomed. Pharmacother. 109 (2019) 1394–1405.

[10] C. Ghosh, J.A. Baker, K.B. Moysich, R. Rivera, J.R. Brasure, S.E. McCann, Dietary intakes of selected nutrients and food groups and risk of cervical cancer, Nutr. Cancer 60 (3) (2008) 331–341.

[11] M. Morris, P.J. Eifel, J. Lu, P.W. Grigsby, C. Levenback, R.E. Stevens, et al., Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer, N. Engl. J. Med. 340 (15) (2002) 1137–1143.

[12] L. Sun, Y. Inaba, K. Sato, A. Hirayama, K. Tsuboi, R. Okazaki, et al., Dose-dependent decrease in anti-oxidant capacity of whole blood after irradiation: a novel potential

marker for biodosimetry, Sci. Rep. 8 (1) (2018) 7425.
[13] S. Kobashigawa, G. Kashino, K. Suzuki, S. Yamashita, H. Mori, Ionizing radiation-induced cell death is partly caused by increase of mitochondrial reactive oxygen species in normal human fibroblast cells, Radiat. Res. 183 (4) (2015) 455–464.
[14] V. Bhuvarahamurthy, N. Balasubramanian, S. Govindasamy, Effect of radiotherapy and chemoradiotherapy on circulating antioxidant system of human uterine cervical carcinoma, Mol. Cell. Biochem. 158 (1) (1979) 17–23.
[15] F. Committee, FIGO staging for carcinoma of the vulva, cervix, and corpus uteri, Int. J. Gynaecol. Obstet. 125 (2) (2014) 97–98.
[16] J.C.S. Paterson, H.S. Wiggins, An estimation of plasma vitamin A and the vitamin A absorption test, J. Clin. Pathol. 7 (1) (1954 Feb) 56–60.
[17] M.E.Y.U. Dju, Chemical Estimation Tocopherol vol. 141, (1948).
[18] K. Karki, D. Pande, R. Negi, R. Khanna, H.D. Khanna, An assessment of oxidative damage and non-enzymatic antioxidants status alteration in relation to disease progression in breast diseases, Med. Sci. 4 (4) (2016) 17.
[19] N. Mut-Salud, P.J. Álvarez, J.M. Garrido, E. Carrasco, A. Aránega, F. Rodríguez-Serrano, Antioxidant intake and antitumor therapy: toward nutritional recommendations for optimal results, Oxidative Med. Cell. Longev. 2016 (2016) 1–19.
[20] T.E. Crane, B.R. Khulpateea, D.S. Alberts, K. Basen-Engquist, C.A. Thomson, Dietary intake and ovarian cancer risk: a systematic review, Cancer Epidemiol. Biomark. Prev. 23 (2) (2014) 255–273.
[21] M. Aghajanpour, M.R. Nazer, Z. Obeidavi, M. Akbari, P. Ezati, N.M. Kor, Functional foods and their role in cancer prevention and health promotion: a comprehensive review, Am. J. Cancer Res. 7 (4) (2017) 740–769.
[22] I. Harris, J. Brugge, The enemy of my enemy is my friend, Nature 527 (7577) (2015) 170–171.
[23] C. Vale, J.F. Tierney, L.A. Stewart, M. Brady, K. Dinshaw, A. Jakobsen, et al., Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials, J. Clin. Oncol. 26 (35) (2008) 5802–5812.
[24] J. Lee, D.H. Lim, S. Kim, S.H. Park, J.O. Park, Y.S. Park, et al., Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial, J. Clin. Oncol. 30 (3) (2012) 268–273.
[25] Y.J. Wu, The chemoprotective agent N-acetylcysteine blocks cisplatin-induced apoptosis through caspase signaling pathway, J. Pharmacol. Exp. Ther. 312 (2) (2005) 424–431.
[26] V. Fuchs-Tarlovsky, M.A.C. Rivera, K.A. Altamirano, J.C. Lopez-Alvarenga, G.M. Ceballos-Reyes, Antioxidant supplementation has a positive effect on oxidative stress and hematological toxicity during oncology treatment in cervical cancer patients, Support. Care Cancer 21 (5) (2013) 1359–1363.

Anju Shrivastava Biophysics

Satyajit Pradhan Radiotherapy & Radiation Medicine

Surendra Pratap Mishra Biochemistry

Anupam Kumar Asthana Radiotherapy & Radiation Medicine

Sunil Choudhary Radiotherapy & Radiation Medicine

Kulsoom Zahra Biochemistry

Lalit Mohan Aggarwal Radiological Physics