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Original Research Article

Study of Various Oxidants and Trace Elements in Cervical Cancer Patients at Tertiary Care Center of Udaipur, Rajasthan, India

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Abstract

Background: Cervical Cancer is one of the most common gynaecological malignancy worldwide. Approximately, 5,00,000 new cases are diagnosed every year with a higher rate of incidence among women of lower socioeconomic status especially in developing countries.

Objectives: The objective of this study is to measure the oxidant status. To estimate and compare serum levels of oxidant MDA (malondialdehyde) and trace elements like Mg, Zn and their derangement in premenopausal and postmenopausal cervical cancer patients

Methodology: These case control studies consist of 150 patients of cervical cancer along with 150 healthy subjects of précised matched age within the institution. blood samples was collected from all participants and samples were analysed for oxidant MDA (malondialdehyde)and trace elements like Mg and Zn. Results obtained were analyzed statistically to see the significance of differences.

Results: The Mean concentration of S.MDA (nmol/L) in case group was 5.88 ±2.52 while that of cervical cancer, MDA, Mg, and Zn control group 2.92 ±0.70 and the difference among them found to be highly significant. Zinc and Magnesium levels were found to be low in cervical cancer patients as compared to control group. The Mean concentration of S. magnesium (mg/dL) was in case group was 1.30±0.44 and 1.91 ±0.29 control group and the difference among them found to be highly significant. Similar to that S. Zinc (mcg/dL) concentration in case group was 35.87 ±11.31 and in control group 118.26 ±29.41. And the difference among them found to be highly significant.

Conclusion: We conclude that an imbalance between oxidant-antioxidant status of patients in case Group when compared to healthy controls. This imbalance plays an important role in the pathogenesis and progression of cervical cancer though the involvement of these parameters is altered in oxidative stress. The study found significantly lower concentrations of zinc and Magnesium in cervical cancer patients. Zinc and Magnesium supplements may therefore result in reduced cervical cancer occurrence among high risk women.

Keywords: Cervical Cancer, MDA, Mg, and Zn

INTRODUCTION

Cervical cancer is the most common cancer in Indian women. Oxidative stress is potentially harmful to cells and ROS are involved in multistage carcinogenesis, in initiation and promotion.[1]

Almost all cervical cancers are caused by high-risk subtypes of the human papillomavirus (HPV), and HPV screening and vaccination programs are effective strategies in disease prevention [2]. HPV causes cervical cancer by damaging DNA, but recent data revealed that oxidative stress plays a role in its development [3]. Chemoradiation is known to improve the survival of patients with cervical cancer. Oxidative stress is an imbalance between the prooxidant-antioxidant systems. A decrease in the level of antioxidants generated free radicals, which leads to DNA damage, causing dysfunction and disease [4]. It is caused by a disturbed oxidant-antioxidant balance in favour of oxidants, leading to excessive generation of free radicals, particularly reactive oxygen species (ROS), and biological damages. Superoxide anion (O_2•−), hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH) are kinds of ROS that are produced by partial reduction of atmospheric O_2 [5]. Malondialdehyde (MDA) is one of the most common markers of oxidative stress and is an oxidant-antioxidant adduct in cancer patients. Lipid peroxidation is initiated by the reactive oxygen species (ROS), which is produced from different processes leading to the production of excessive MDA, which in turn changes the normal cell functioning and causes cancer [6]. The high level of MDA concentration can be ascribed to a higher production of ROS due to a rise in the oxidative damage in patients of uterine cancer. In the progression of disease, the production oxygen radical also increases, which in turn increases lipid peroxidation. This process results in the damage or degeneration of cell membrane and DNA.

Trace elements such as copper (Cu), Magnesium (mg) Magnesium (Se), manganese Mn), iron (Fe), zinc (Zn) play an important role in cancer prevention [7]. These elements act as co-factors for Antioxidant enzymes. The essential trace elements have anti-cancer properties, and they exert their chemopreventive effect by aiding in the synthesis of antioxidant enzymes and removing the reactive oxygen species (ROS).

The aim was to study the alterations in the circulating pro-/anti-oxidants in advanced cervical cancer patients.

METHODS

This case control study will be conducted on 150 patients of cervical cancer who are visiting Gynaecology OPD of PDZ Hospital, Udaipur. The control group will be consisting of 150 healthy subjects of précised matched age within the institution.

Exclusion criteria: include late pregnancy, any other carcinoma of female reproductive system, DM, supplementations of vitamins.

Inclusive criteria: as mentioned above all consecutive patients with positive Pap smear are to be enrolled.

The same inclusive and exclusive criteria are to be applied for control subjects as well. All the above exclusion factors will be confirmed from the patient reports and history.

Patients that are coming to Gynecology OPD and patients with positive Pap smear will be enrolled. Selection of cases is to be based on detailed inclusion & exclusion criteria and clinical history.10 ml blood sample will be collected through venepuncture under aseptic precautions in sterile plain and EDTA vial. Samples will be incubated & centrifuge at 3000 rpm for 15 minutes. Precautions will be taken to avoid haemolysis & other contamination &

separated serum will be analysed for test like MDA (malondialdehyde) Mg and Zn Results obtained were analysed statistically to see the significance of differences by calculating p value by using online student t-test calculator.

RESULTS

These case control studies consist of 150 patients of cervical cancer of age Group from 30-60 year along with 150 healthy subjects.

The mean age of cervical cancer group (case) is 51.26±10.43 year while that of control group is 44.87±12.52 year.

Table 1: Age wise distribution of the participants

Parameters	Case (n=150)	Control(n=150)	P value
Age	51.26 ±10.43	44.87±12.52	0.07

(P value <0.001 significant)

Table 2: Demographic characteristics of the participants

Parameters	Case (n=150)	Control (n=150)
Hindu	148(98.66%)	144(96%)
Muslim	2(1.3%)	4((2.6%)
Smoking	12(8%)	15((10%)
Alcohol	10(6.6%)	13(8.66%)
Married	138(92%)	131(87.33%)

(P value <0.001 significant)

According to demographic data, Religion wise 98.66% of cervical cancer patients were Hindu and 96% controls were Hindu. Smoking history present in 8% and 10% in case and control group respectively. History of alcohol present in 6.6% and 8.66% in case and control group respectively. (Table 2)

Among total 150 patients of cervical cancer 138(92%) females were married.

Table 2A: Demographic characteristic of the participants

Parameters	Case (n=150)	Control (n=150)
Rural residence	139(92.66%)	51(34%)
urban residence	13(8.66%)	99((66%)
Family history present	38(25.33%)	08((5.3%)
Family history not present	114(76.0%)	142(94.66%)
Married	138(92%)	131(87.33%)

Table 3: Education wise distribution of case and control group

Parameters	Case (n=150)	Control (n=150)
Illiterate	106(70.66%)	37(24.66%)
Literate	16(10.66%)	74(49.33%)
Semi-literate	30(20.0%)	39(26.0%)

Table 4: Distribution of the participants based on BMI

Parameters	Case (n=150)	Control (n=150)	P value
Weight(kg)	53.13 ±7.9	61.78 ±7.42	0.56
Height(cm)	165.1±5.0	162.56 ±4.0	0.95
BMI	19.53 ±1.0	23.54 ±1.2	0.86

P value <0.001 significant

Average BMI of control group were 23.54 ±1.2, while that of case were 19.53 ±1.0 but difference among them were not found to be significant because p value is <0.05. (Table 4)

Table 4: Showing comparison of MDA and trace elements Levels between case and control group

Parameters	Case (n=150)	Control (n=150)	t-value	P value
S. MDA *(nmol/L)*	5.88 ± 2.52	2.92± 0.7	13.86	<0.001*
S. Magnesium (mg/dL)	1.3 ± 0.44	1.91± 0.29	14.17	<0.001*
S. Zinc(mcg/dL)	35.87± 11.31	118.26 ± 29.41	32.02	<0.001*

P value <0.001 significant *Significant

The Mean concentration of S.MDA *(nmol/L)* in case group was 5.88 ±2.52 while that of control group 2.92 ±0.70 and the difference among them found to be highly significant.(Table 4) The Mean concentration of S. magnesium (mg/dL) was in case group was 1.30±0.44 and 1.91 ±0.29 control group and the difference among them found to be highly significant. similar to that S. Zinc(mcg/dL) concentration in case group was 35.87 ±11.31 and in control group 118.26 ±29.41. (Table 4) and the difference among them found to be highly significant. Serum ferritin concentration in case group was 160.13 ±89.67 while that of control group 170.03 ±71.71 and p-value is 0.2918 so the difference among them is not significant while the level of S. Vitamin B12 was 499.97 ±284.4 and 352.18 ±169.22 in case and control group respectively and the difference among them found to be highly significant. (Table 4)

DISCUSSION

Oxidative stress (OS) results from an imbalance in the formation and elimination of oxidant species. Accumulation of these molecules may lead to cell dysfunction as a consequence of accumulated oxidative modifications in several biomolecules. [8] Free radical generation represents a continuous physiological process that results from biological functions, including metabolism and inflammation. In the mitochondria, cytochrome P450 and peroxisomes are the major endogenous factors leading to reactive oxygen species (ROS) and reactive nitrogen species (RNS) formation. Other exogenous factors, such as radiation, tobacco smoking, chemotherapy and diet, are also important inductors of free radical production[9]. Intermediate reactive species that are naturally produced under physiological conditions have a crucial role in metabolic regulation, the cell cycle and intracellular signaling pathways.

Czapp et al (2010) founded that low magnesium will negatively affect permeability of the cell, and have suggested that this can initiate carcinogenesis.[10] Thissiane L. Gonçalves et al. (2005) founded that in cervical cancer patients, regardless of disease state, pre-malignant (low squamous intraepithelial lesion—LSIL and high squamous intraepithelial lesion—HSIL) or cancer, showed a significant 2–3 times increase in TBARS levels (P > 0.01) when compared to healthy controls (P < 0.01). [11]

In addition to HPV infection, several cofactors contribute to cervical cancer development. These include low socioeconomic status, early sexual initiation, multiple sexual partners, smoking, multiparity, immunosuppression and use of oral contraceptives[12]. Cervical cancer is mostly a consequence of the continuous evolution of non-invasive precursor lesions called cervical intraepithelial neoplasia (CIN) that are characterized by different degrees of cellular atypia (dysplasia) [13]. CIN is divided into the following groups: CIN 1, characterized by mild dysplasia; CIN 2, which represents moderate dysplasia; and CIN 3 or carcinoma in situ, characterized by a severe dysplasia that may progress to an invasive squamous cell carcinoma

(SCC). Moreover, changes in the glandular epithelium of the cervix, caused by HPV and other cofactors, are associated with the development of cervical adenocarcinoma [14]. Furthermore, in persistent viral infection, HPV-induced carcinogenesis involves genetic and epigenetic changes that affect the expression of different cellular proto-oncogenes and tumor suppressor genes. Usually, this process requires an extensive period to accumulate sufficient alterations to trigger and sustain tumor development[15]. Therefore, immune system evasion and HPV persistence are crucial factors for tumorigenesis. This is highlighted by the fact that the great majority of HPV infections are self-limited and spontaneously resolved in few months, and cancer development affects only a small proportion of infected individuals. Alterations in expression and activity of some antioxidant proteins, including peroxiredoxins, catalase, quinone oxidoreductase-1 and superoxide dismutase (SOD) family proteins, can be detected in pre-neoplastic and neoplastic tissues associated with HPV infections. For example, expression of SOD2, a crucial antioxidant enzyme responsible for controlling the redox status of normal and tumor cells, is upregulated in several HPV-associated tumors, including penile and cervical carcinomas[16,17]. Furthermore, results from different studies have established that the HR-HPV E6 and E7 oncoproteins can modulate OS to favor the accumulation of mutations, a fact that is directly related to cell transformation

Deheinzelin et al (2000) found that almost half of cancer patients admitted to the ICU had low magnesium levels. Magnesium deficiency may have contributed to their disease but it may infact also be due to their cancer treatment. [18]

C. DeMarco et al (2015)stated that the use of birth control pill leads to several nutritional deficiencies, most notably of folic acid. However other can occur, including vitamin C, B2, B6, B12 andzinc. [19]

In this study, we investigated the levels of three serum trace elements in patients with histologically diagnosed cervical cancer compared with cancer-free controls The findings from our present study indicated a strong association of low serum levels of Zinc and Magnesium with invasive squamous cells carcinoma of the cervix. Previous studies, just like this current study, have also reported that serum Zinc concentrations were decreased in patients with ovarian, testicular, cervical, bladder and renal cancer [20]. Zinc plays an anti-carcinogenic role through structural stabilization of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and ribosome. It has a protective effect against free-radical injury. Our study just like some other epidemiologic studies revealed that a low Magnesium level in serum increase the risk of human cancers such as cancer of the stomach, oesophagus, colon, lung, prostate and breast [21]. It has been suggested that Magnesium protects cell by inhibiting free oxygen radical production. Moreover, an important antioxidant Vitamin E is transported by selenoproteins. Magnesium has been shown to possess cancer-preventive and cytoprotective activities in animal models and humans . In our study, even though the mean serum concentration of Copper in the cancer patients was higher than in the controls, we did not find any statistically significant association. Copper plays a role in the production of haemoglobin, myelin, collagen and melanin as an essential nutrient and studies have shown that normal immune function requires adequate Cu intake[21]. However, serum copper values are significantly elevated in many disease conditions such as chronic obstructive pulmonary disease (COPD), malignancies and psychosis. The major limitations to this study were that it was hospital-based and thus the findings may not be generalizable to the public and also the study design will not allow us to

conclude if Zinc and/or Magnesium deficiencies actually preceded or occurred as a result of cervical cancer.

CONCLUSION

We conclude that an imbalance between oxidant-antioxidant status of patients in case Group when compared to healthy controls. This imbalance plays an important role in the pathogenesis and progression of cervical cancer though the involvement of these parameters is altered in oxidative stress. The study found significantly lower concentrations of zinc and Magnesium in cervical cancer patients. Zinc and Magnesium supplements may therefore result in reduced cervical cancer occurrence among high risk women.

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