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Critical Review on Role of Some Nutritional Components in Prevention of Cancer In India: An Educators Role

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Abstract

Carcinogenesis, in a recent years, is highly known to be linked with nutrition, particularly the micronutrients which play an important role as an antioxidant as well as an immunity-potentiating agent. Epidemiological studies with human cancer subjects, however, were very limited in India though people in India are exposed to different kind of carcinogens quite often. In this review, we analyzed and showed that Vitamin C, Vitamin E and Zinc have significant effect in lowering cancer risk. The vegetables and fruits that are rich in Vitamin C are broccoli, Brussels sprouts, cauliflower, green and red peppers, spinach, cabbage, turnip greens, and other leafy greens, capsicum, Lemon, oranges, etc. Food rich in Vitamin E are nuts, seeds, avocado, vegetable oils and wheat germ. Zinc, an important trace elements for growth can be found in meat, shellfish, legumes like chickpeas, lentils and beans, seeds, nuts, dairy, eggs and whole Grains Our mission, as an educators and researchers, is to translate the scientific discovery of any health issue like cancer to a health-literate generation in college, family, and community. Coordinated collaboration between professionals in education and public health can better prepare our young people to be health literate and cancer-free.

Keywords: Nutrition; Cancer; Epidemiology; Prevention; Antioxidants; Vitamins; Copper; Selenium; Zinc; Health Education.

Abbreviations: OR: Odds Ratio; CI: Confidence Interval

Introduction

Dietary factors particularly micronutrients play an important role in the carcinogenesis pathway owing to their antioxidant action as well as immunity potentiating effect. Most of the studies attempted to assess the carcino-protective role of Vitamins and Minerals in various animal models and in vitro cell lines. Replicability of findings of such studies in human subjects is not beyond question. However, epidemiological studies on human subjects such as cancer patients and controls were conducted in different countries but in relatively limited numbers. Such studies in Indian population and perspective are even lesser. People in India are exposed to different kind of genetic and environmental risks for cancer compared to developed countries [1–3]. Similarly dietary pattern of Indian people are also different from other Asian and European countries. Variation of dietary diversion also exists within different parts of India, particularly with regards to consumption of micronutrients in their regular diets [4, 5]. Regarding the role of vitamins and minerals in cancer, different findings were observed in different studies, such as role of selenium was found to increase as well as decrease the risk owing to role in different biochemical pathways [6–8].

Similarly different studies in Indian population found different evidences of the carcino-protective role of various micronutrients presents in Indian diets and spices, one such an example is turmeric (Curcumin) [9–16]. Curcumin, (bis-α, β-unsaturated β-diketone) actually present in the Indian spice "haldi", and it affects against cancer. Curcumin promotes apoptosis, scavenges reactive oxidative species (ROS), and reduces the inflammatory cancer microenvironment, and thereby is considered for chemoprevention of multiple cancers [17].

Hence, this critical review will attempt to find how strong is the evidence of risk reduction effect of micronutrients in regards to various cancers in Indian perspective.

In this review, we analyzed the methods and results of six original research articles based on studies on Indian patients. Out of these six studies, two were on Oral cancer including premalignancies by Shishir Ram Shetty et al, 2013 [18]; and Amith Kumar et al, 2014 [19], one each on breast cancer by Preeti Singh et al. 2005 [20], laryngeal cancer by Kapil U et al, 2003 [21], gastric cancer by Madhuri K et al, 2011 [22]; and colorectal cancer by Sunil Chandy et. al, 2008 [23].

Materials and Methods

Relevant articles were searched in Pubmed database (Pubmed Central- NCBI) as well as Google search.

Key words used in the search were Protective Effect, Micronutrient, Cancer, India. A total of around 95 articles were found; 65 from Pubmed, and 30 additional articles by Google search other than those found in Pubmed. Following selection criteria were used to choose the articles for the current review:

1) Those are original articles

2) Those are based on human subjects (patient, controls etc.) i.e. in vivo studies.

3) Those have been conducted on Indian population

4) Those have been published in the year 2000 and after.

5) Articles only on pre-malignancies were excluded

A total of 6 such full articles were found and considered for the review.

Detailed Methods of Each Study

1) In the Case control study by Shishir Ram Shetty et al (2013), 4 equal groups (50 persons in each) were chosen comprising of cases of Oral Leukoplakia, Oral Sub mucous Fibrosis, Oral Squamous Cell Carcinoma and Healthy Controls [18]. Mean serum levels of Copper and Zinc were compared by ANOVA.

2) In the hospital based Case Control study by Amith Kumar et al, (2014), 60 histopathologically confirmed cases of oral cancer were considered with an age range of 22 to 77 (Median 57) along with 13 cases of premalignancy [19]. Cases taking medication and antioxidant supplements were excluded. 70 controls were taken (age- 20 to 68 years). They were not associated with smoking, alcohol and recent diet change.

Serum level of iron, zinc, copper, selenium and hemoglobin were assayed and mean levels of them were compared between cases and controls by unpaired t-test.

3) The study by Preeti Singh et al (2004) was also a hospital based case- control study where 160 cases of histology or cytology confirmed breast cancer and same number of controls were chosen from outpatient and inpatient Dept., AIIMS, New Delhi [20]. Only those cases were included where no specific treatment was given for breast cancer and those who had not suffered from any other chronic disease leading to change in dietary pattern. Mean serum level of Vitamin C, E and selenium level were measured by standard procedures and the data were analyzed by unpaired

t- test, Odds Ratio (OR) and 95% Confidence Interval (CI).

4) The Study by Kapil U, et. al. (2003) was also a hospital based case- control study where 155 cases of histopathology confirmed laryngeal cancer and same number of controls were chosen from outpatient and inpatient Dept. of Otorhinolaryngology and head & neck tumor clinic AIIMS, New Delhi [20]. Controls were matched for age group, sex and residence matched. The inclusion criteria of cases were similar to earlier studies such as - not undergone specific treatment, no change in diet no micronutrient supplements, not suffering from other major illnesses or not corticosteroid therapy. Controls were unrelated to cases and also fulfill other criteria of cases except for having cancer. Estimation of Vitamin A, C and Zinc level was measured following standard procedures. Unpaired t- test was used for comparing the mean serum level of micronutrients between cases and matched controls. Univariate Logistic regression was also carried out to measure odds ratio (OR) and 95% Confidence Interval (CI).

5) The study by Madhuri K, et. al. (2011) was also a hospital based case control study where 80 cases of gastric cancer from South India, receiving adjuvant chemotherapy (a combination of Epirubicin, Cisplatin and 5- flurouracil) were selected along with 100 healthy controls [22]. Mean age group of the cases was in the range of 46 - 50 years. Vitamin C prophylaxis was given in a daily dose of 1 gm for five days in a week for 3 months. Blood samples were collected before and after Vitamin C Prophylaxis and Cytogenetic studies (Chromosomal aberrations and Sister Chromatid Exchanges) were carried out on lymphocytes using standard protocols. The Student- t test was used to analyze the difference in frequency of mean Chromosomal aberrations and Sister Chromatid Exchanges per cell between cases and control as well as before and after Vitamin C prophylaxis. It was assumed that number of Sister Chromatid Exchanges per cell is very small, hence followed the Poisson distribution.

6) The study by Sunil Chandy, et. al. (2008) is a case control study where 30 patients of histologically confirmed colorectal cancer were considered irrespective of stage and prior to treatment [23]. Same number of age and sex matched controls were taken in the study. Vitamin B12 and folate levels were analyzed and expressed as mean + SD. Independent t test was used (two tailed) to measure the difference between two groups.

More Study Findings in details

1) Mean copper level was significantly higher in Oral Submucous Fibrosis (310.61 $\pm$ 4.22 µg/dL) group compared to control. For other groups although this level was higher than control (196.54 $\pm$ 3.76µg/dL). but the association was not significant. Mean zinc level was significantly lower in all the three study groups compared to controls. Copper - Zinc ratio was found to be higher in all the three study groups, however serum iron level was lower in them.

2) Mean serum level of zinc and copper was found significantly ($p<0.001$) lower in oral cancer cases compared to controls. On the contrary, mean serum level of selenium was significantly ($p<0.001$) higher among cases (0.12 $\pm$ 0.04 µg/dL compared to 0.10 $\pm$ 0.01 µg/dL in controls). No significant difference was found in the level of serum iron and hemoglobin. However, in precancerous cases only serum copper level was significantly lower ($p<0.01$) than controls.

3) Mean age of cases and controls were respectively 45.29 $\pm$ 10.64 and 40.98 $\pm$ 10.32 years. All of them were married and around 95% were housewives. Mean serum level of Vitamin C was found significantly lower in cases (0.68 $\pm$ 0.45 mg/dL) compared to controls (1.09 $\pm$ 0.50 mg/dL). An Odds Ratio (OR) of 0.16 (0.09 - 0.27) implies 84 % risk reduction of breast cancer with 1 unit rise in serum Vitamin C level. Similarly in case of Vitamin E, significantly lower values were observed in the cases and a 77% risk reduction (OR = 0.23, 95% CI: 0.15 - 0.33) was observed. Serum selenium level also showed 7% risk reduction but this association was not found significant (OR = 0.93, 95% CI: 0.72 - 1.22).

4) About 89% cases were male and most of them belonged to age group of 41- 60 years. Mean serum level of Vitamin A was significantly lower in laryngeal cancer cases compared to controls. Significant difference was also observed in mean serum level of Vitamin C and Zinc levels. Maximum cancer risk reduction (42%) was found with Vitamin C (OR = 0.58). Risk reduction associated with Vitamin A (2%) and Zinc (1%) was very much lower.

5) The % of chromosomal aberrations before Vitamin C Prophylaxis was significantly ($t = 11.11$, $p <0.001$) higher in cases (10.13 $\pm$ 5.54) than in controls (3.65 $\pm$ 1.63). Total aberrations decreased significantly ($t = 9.39$, $p <0.001$) in cases following 3 months of Vitamin C prophylaxis (6.10 $\pm$ 2.72), however no significant difference was observed in controls. Similarly mean Sister Chromatid exchange per cell was also significantly ($t = 32.32$, $p <0.001$) higher in cases (9.27 $\pm$ 0.14) than controls (3.30 $\pm$ 0.04) before Vitamin C administration and it was reduced significantly ($t = 9.39$, $p <0.001$) after Vitamin C prophylaxis

Results

Study findings are shown in the Table below:

Authors & Year	Topic	Type of Study	Focused Nutrients	Results	Findings
Shishir Ram Shetty et al, 2013 [18]	Role of Serum Trace Elements in Oral Precancerous and Oral Cancer – A Biochemical Study.	Case control study	Zinc, and Copper	Mean Copper level was significantly higher in oral sub mucous fibrosis (310.61 ± 4.22 µg/dL) compared to Control (196.54 ± 3.76µg/dL). Mean Zinc level (110.11 ± 2.83µg/dL) was significantly lower in cases compared to Controls (162.07 ±2.91µg/dL).	Copper - Zinc ratio was found to be higher (2.1 in OSMF, 1.32 in Oral Leucoplakia, 2.91 in Oral Squamous Cell Carcinoma) in the pre-cancer and cancer cases compared to Controls (1.21).

Table-1

Authors & Year	Topic	Type of Study	Focused Nutrients	Results	Findings
Amith Kumar et.al, 2014 [19]	Estimation of Serum Micronutrient Levels and The Possible Risk of Oral Cancer and Pre-malignancy	Hospital Based Case Control Studies	Zinc, Copper, Selenium, Iron	1) Mean serum level of Zinc (31.4±5.82 µg/gm Hb) and Copper (109.76±25.58 µg/dL) was significantly lower ($p<0.001$) in oral cancer cases compared to Controls (Zn: 35.6±6.25 µg/gm Hb And Cu: 180.9±5.48 µg/dL). Mean serum level of Selenium was significantly higher ($p<0.001$) among Cancer cases (0.12 + 0.04 µg/dL) compared to in Controls. (0.10 + 0.01nµg/dL). No Significant Difference found in Serum Fe level.	Zinc and Copper was found protective for Cancer. Selenium was found to increase the Risk. No significant effect was found with serum Iron Level.

Table-2

Authors & Year	Topic	Type of Study	Focused Nutrients	Results	Findings
Preeti Singh et.al, 2005 [20].	Association between Breast Cancer and Vitamin C, Vitamin E and Selenium Levels: Results of a Case- Control Study in India	Hospital based case control study	Vitamin C, Vitamin E and Selenium	Mean serum levels of Vitamin C (0.68±0.45 mg/dL) and Vitamin E (0.92 + 0.68 mg/dL) in breast cancer patients are significantly lower than control. For Vit C, the OR=0.16, 95% CI: 0.09 - 0.27. And for Vit E the OR =0.23, 95% CI : 0.15 - 0.33). No significant difference was found in the mean serum level of Selenium.	84% and 77% risk reduction were observed respectively with Vitamin C and Vitamin E. Selenium was not found to have a significant protective effect.

Table-3

Authors & Year	Topic	Type of Study	Focused Nutrients	Results	Findings
Preeti Singh et.al, 2005 [20].	Association between Breast Cancer and Vitamin C, Vitamin E and Selenium Levels: Results of a Case- Control Study in India	Hospital based case control study	Vitamin C, Vitamin E and Selenium	Mean serum levels of Vitamin C (0.68±0.45 mg/dL) and Vitamin E (0.92 + 0.68 mg/dL) in breast cancer patients are significantly lower than control. For Vit C, the OR=0.16, 95% CI: 0.09 - 0.27. And for Vit E the OR =0.23, 95% CI : 0.15 - 0.33). No significant difference was found in the mean serum level of Selenium.	84% and 77% risk reduction were observed respectively with Vitamin C and Vitamin E. Selenium was not found to have a significant protective effect.

Table-3

Authors & Year	Topic	Type of Study	Focused Nutrients	Results	Findings
Kapil U et al, 2003 [21].	Association of Vitamin A, Vitamin C and Zinc with Laryngeal Cancer	Hospital based case- control study	Vitamin A, Vitamin C and Zinc	Maximum cancer risk reduction (42%) was found with Vitamin C (OR= 0.58). Risk reduction associated with Vitamin A (2%) and Zinc (1%) were very much lower.	Vitamin C, Vitamin A and Zinc were found to have significant protective effect.

Table-4

Authors & Year	Topic	Type of Study	Focused Nutrients	Results	Findings
Madhuri K et al, 2011 [22].	Role of Ascorbic Acid as an Antioxidant in Gastric Cancer Patients in South Indian Population	Hospital based case control study	Vitamin C	Total chromosomal aberrations as well as sister chromatid exchange per cell decreased significantly (t =9.39, p <0.001) in cases following 3 months of Vitamin C prophylaxis. No such difference was found in controls.	Vitamin C prophylaxis in cancer patient has a significant effect in reducing chromosomal aberrations.

Table-5

Authors & Year	Topic	Type of Study	Focused Nutrients	Results	Findings
Sunil Chandy et. al, 2008 [23].	Effect of Vitamin B12 and Folate on Homocysteine levels in Colorectal Cancer	Case Control study	Vitamin B12, Folic acid	Mean folate levels in cases and controls were 10.30 ± 7.05 ng/mL and 10.53 ± 3.99 ng/mL, respectively. (p=0.90). Mean Vitamin B12 levels were 419.76 ± 281.70 pg/mL in cases and 239.41± 116.58 pg/mL in Controls (p =0.014)	Vitamin B12 levels were significantly higher in cases. No significant difference in folate level between cases and controls.

Table-6

OR: Odds Ratio; CI: Confidence Interval

among the cases.

6) Mean age of cases and controls were respectively 39 and 40 years. Out of 30 cases, 12 were of colon cancer and 18 of rectal cancer. Mean folate levels in cases and controls were 10.30 ± 7.05 ng/mL and 10.53 ± 3.99 ng/mL (p =0.90). Mean vitamin B12 levels were 419.76 ± 281.70 pg/mL in cases and 239.41±116.58 pg/mL in controls (p = 0.014).

Discussion

Most of the studies discussed here, compared the mean levels of micronutrients in the cases and controls. Mostly micronutrient levels were found to be significantly lower in cases than in controls, thereby establishing a risk reducing effect.

In the above studies, Vitamin C and Zinc were the most commonly studied vitamin and mineral. All the studies discussed here found a significant protective effect of Vitamin C and Zinc. However in case of copper, one study Amith Kumar et al. (2014) found it as a protective factor for oral cancer [19], whereas another study by Shishir Ram Shetty, et. al. (2013) found the reverse [18]. However, Copper to Zinc ratio was observed as a reliable predictor for cancer risk. Regarding the role of Selenium, one study found it as a risk factor for cancer (higher level of cases) [18], and another study did not elicit any significant relationship [19]. Among other vitamins, Vitamin A and E were also found to have significant cancer risk lowering effect. Strangely, in one study Vitamin B12 level was found much higher in cases of colorectal cancer [23]. No significant role of Iron and Folic acid was found in these studies.

Vitamin C was found to be associated with highest risk reduction (84% in one study and 42% in another). Chromosomal aberrations were also reduced significantly in gastric cancer cases following 3 months of Vitamin C prophylaxis [22]. Vitamin E was found to have the next higher protective effect (77% risk reduction). Vitamin A and Zinc showed very little risk reduction.

Most of the studies measured the effects of micronutrient in terms of Odds Ratio (OR< 1 is protective). However, the temporality of such association was subject to assessment i.e. whether lower micronutrient levels led to cancer or cancer caused reduction in the serum levels. Only one study [22] (Madhuri et. al., 2011) estimated the changes in mean frequencies of chromosomal aberrations before and after vitamin C prophylaxis in gastric cancer cases and controls. Significant reduction after prophylaxis in cases may be an important finding but this was the effect of Vitamin C on the already established cancer cells, which are rapidly, dividing with an enhanced rate of DNA replication, damage and repair.

Mostly studies measured the mean serum level of micronutrients among cases and controls and compared by t test. However, it is not documented how much difference in mean level is clinically significant to enhance risk of any particular cancer and it may vary with different micronutrient also.

Also in many of the studies, only few micronutrients were assessed and their effect were analyzed by univariate methods (OR and 95% CI) whereas their combined effect actually counteract the carcinogenesis process at molecular level.

Regardless of the weight of causative factors of cancer, the more useful resource to control this problem at the population level is prevention of the disease [24] (Bray et al., 2012). As a researcher as well as an educator we believe the learning in preventive measures is important to sensitize individuals to campaigns against cancer that includes health education and early detection of cancer.

It is undeniable that in breast and cervical cancers (BC/CC), the lack of information on early detection of cancer and ignorance of risk factors, have caused the high female mortality. It is necessary to sensitize women, and this is extremely important in India and other countries where these neoplasms are the first causes of mortality. It is also essential to educate men about the importance of early detection [25] (Thiel de Bocanegra et. al., 2009). We believe that awareness should start in early stages in both genders.

The proposal of implementing health education modules for the parents and teachers of young children and middle school adolescent students, as they are mature enough to receive and understand the concept and to apply knowledge related with cancer prevention [26] (Yadav and Jaroli, 2010). It is not a chance or random event, rather a planned outcome of the well-designed, well resourced, and sustained health education in the nation's schools for the healthy and well-being of our nation's young people. We researched food that are rich in Vitamin C, E and zinc to educate the community. Vegetables with the highest sources of vitamin C include: broccoli, Brussels sprouts, cauliflower, green and red peppers, spinach, cabbage, turnip greens, and other leafy greens. Sweet and white potatoes, tomatoes and winter squash. Food rich in Vitamin E include: nuts, seeds, avocado, vegetable oils and wheat germ. Some dark leafy greens

and fish are also sources of vitamin E. The ten food that are high zinc include: meat, shellfish, legumes like chickpeas, lentils and beans, seeds, nuts, dairy, eggs and whole Grains.

Our mission, as an educators and researchers, is to translate the scientific discovery of any health issue like cancer, to a health-literate generation in college, career, family, and community. Coordinated collaboration between professionals in education and public health can better prepare our young people to be health literate and cancer-free.

Conclusion

In this review, Vitamin C, Vitamin E and Zinc were found to have the significant effect in lowering cancer risk. However, further studies are required to establish combined effect of different micronutrient as well as temporality of the relationship.

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