Date received: August 1994

Diet and oral cancer - a case control study

MPR. Prasad*, TP Krishna*, S Pasricha*, MA Quereshi**, K Krishnaswamy*

*National Institute of Nutrition, Hyderabad; **MNJ Cancer Hospital, Hyderabad

Apart from strong genotoxic carcinogens, other environmental factors are implicated in both causes and prevention of cancers. A hospital based case control study was conducted to examine the role of diet in the aetiology of oral and oropharyngeal cancers. In this article, past dietary intake and nutrient estimates, obtained through diet history method and biochemical nutritional status at the onset of the disease are presented. The results of the study suggest that poor dietary intake of vegetables and fruits coupled with low estimated intake of betacarotene, thiamine, riboflavin, folate, vitamin C, iron and copper, modify the risk potential. The biological indicators of the nutritional status such as plasma vitamin A, E, red cell folate and plasma zinc were significantly reduced in cases and yielded moderate risk estimates. The risk estimates though of moderate magnitude are of importance in relatively homogeneous subjects with respect to diet and nutrition.

The findings are in line with several other epidemiological observations. The combined effects of micro nutrients appears to be protective in countering the adverse effects of exogenous exposures to tobacco. The protective role of vegetables and fruits is of potential interest in terms of etiologic causes and prevention.

Introduction

Oral cancer is one of the ten most common cancers in the world[1]. In India it accounts for a third of all cancers[2]. It is documented in all parts of India. Tobacco smoke and betel chewing with or without tobacco are suggested as etiologic factors accounting for 90% of all oral cancers[1]. The mortality and morbidity of oral cancers are well documented in India. In fact tobacco related cancers seem to be a leading cause of cancers in the whole of the Indian sub-continent[2]. The mortality of oral cancers despite advances in treatment and management appear to be high with poor chances of survival.

Though environmental exposure to tobacco and other carcinogens are important determinants of cancer, it is now well documented that other factors such as diet have an important role to play in the multistage carcinogenesis process. Several dietary factors act as risk modifiers[3-7]. In general though, dietary deficiencies have not been shown to initiate events, epidemiological and experimental studies provide strong evidence for dietary substance, in promotion, progression and inhibition of cancer[8,9].

World wide epidemiological data suggest a strong protective role for fruits and vegetables[10,11]. The protective effects of these in addition to non nutrients have been attributed to micronutrients such as vitamin A, β carotene, folate, vitamin E and vitamin C[12]. Limited observation suggest that probably zinc and selenium deficiencies are also causally related[13-14].

The surveys conducted by NNMB in 10 states of India document poor consumption of green leafy vegetables and also poor intake of vitamins A, C, folate and riboflavin in population groups[15]. As early as 1933, Orr in his classical description of oral cancer in India attributed vitamin A deficiency as one of the important contributing agents[16]. As there is meagre information on the dietary and nutritional correlates of oral cancer in India, a case control study of oral and oropharyngeal cancers was envisaged. The objectives of the study were to :

1. quantitate past dietary intake of food groups and nutrients
2. estimate the nutritional status at the onset of the disease and arrive at risk estimates.

Materials and methods

Cases :

The cases were patients of oral cancer, who presented themselves for the first time at the Government Cancer Hospital (Mehdi Nawab Jung) Hyderabad. Advanced cases and those who received treatment elsewhere were deleted. In all, 45 subjects of both sexes were included after excluding those who had previously consumed vitamin or mineral pills for several days.

Controls:

The controls were carefully matched for age, sex, socioeconomic status and habits and were drawn from attendants of the cancer patients or from patients suffering from non cancerous or other minor ailments.

A detailed clinical, anthropometric and personal history was taken and 10ml blood sample collected in an heparanised tube for biochemical analysis. A dietary history, using standard dietary cups were obtained from compliant individuals participating in the study.

Dietary details:

Dietary consumption pattern over the last six months was assessed by an oral questionnaire. The questionnaire was designed to obtain information regarding the dietary

Correspondence address : Dr. Kamala Krishnaswamy
National Institute of Nutrition, Jamai Osmania P.O.
Hyderabad ,500 007 India
Tel: +91-40-868909 Fax: +91-40-869074

habits. Average frequency of consumption of food items in the preceding six months or before the change in the dietary habit and quantities of different food groups were obtained. From the frequency of consumption, number of food items consumed per month were obtained.

Biochemical Analysis:

Haemoglobin and albumin were estimated by cyanmethaemoglobin and dye binding methods respectively[17,18]. RBC folate was estimated micro-biologically using L. Casei[19]. Riboflavin and thiamin levels were estimated indirectly by measuring the erythrocyte glutathione reductase (EGR) and erythrocyte transketolase (ETK) activity and expressed as activity coefficients[20,21]. High pressure liquid chromatography was used for plasma vitamin A, vitamin E was determined by thin layer chromatography[22,23]. Serum iron was estimated colorimetrically while the trace metals, copper, magnesium and zinc were estimated by atomic absorption spectrophotometry[24,25].

Statistical Analysis:

The Mann-Whitney test was applied for comparisons of means between the two groups[26]. Odds ratios (ORs) were computed (using control values as cut off points) after the intake of nutrients were adjusted for total calorie intake[27,28]. Wherever significant odds ratios were observed, 95% confidence intervals (CI) were also included.

Table 1. Age, weight, site of cancer, and TNM classification

	Cases	Controls
Age (years)	53.9±1.7	53.5±1.8
Weight (kg)	45.2±1.29	49.3±1.38
Site of cancer		
a) Tongue	18	
b) Oral cavity	19	
c) Oropharynx	8	
Number of cases by TNM classification		
$T_1N_0M_0$	8	
$T_1N_1M_0$ $T_2N_0M_0$	10	
$T_2N_1M_0$ $T_2N_2M_0$	20	
$T_2N_1M_1$ $T_2N_2M_1$	2	
$T_1N_1M_0$ $T_3N_1M_0$	5	

Values Mean ± SD. No. of subjects in each group = 45

Results

The mean age in our study was 54 years. More than 90% were either tobacco smokers or tobacco chewers. Smoking was a consistent feature. None of the patients had the habit of reverse smoking. The distribution of cancers by sites are given in Table 1. The body weights of patients varied between 31.0 to 67.0kgs and a mean weight of 45.2±1.29kgs and the mean body mass index (BMI) was 0.17±0.003. The controls had a mean weight of 49.3±1.38kgs and mean BMI of 0.19±0.005 as shown in Table 2.

Table 2. Blood nutrients and other parameters

Parameter	Case	Control
Body mass index	0.17±0.003**	0.19±0.005
Haemoglobin g/ l	120.5±1.97	123.2±1.85
Albumin g/ l	32.3±0.45**	34.6±0.40
RBC folate nmol/ l	277.4±4.79*	295.3±6.54
EGR (AC)	1.27±0.019	1.25±0.018
ETK (AC)	1.22±0.019	1.20±0.02
Vit A µg/ dl	27.3±1.9**	39.6±1.66
Vit E µg/ dl	570.0±34.5***	920.6±57.97
Serum iron µmol/ l	16.5±0.94	16.9±0.47
Copper µmol/ l	19.9±0.35	19.9±0.50
Magnesium µmol/ l	1.4±0.037**	1.2±0.033
Zinc µmol/ l	9.8±0.21***	14.2±0.58

Values are mean ± SE. No. of observations 45 in each group
* p<0.02 **p<0.005 ***p<0.001

The protein energy status as reflected by serum albumin was significantly lower than that of controls (Table 2). More than 60% of the cases were in first tertile (Fig. 1). The haemoglobin levels and the serum iron status were not different between cases and controls.

Figure 1. Tertile distribution of percent cases and controls for serum albumin. (p<0.05) and RBC folates (p< 0.05)

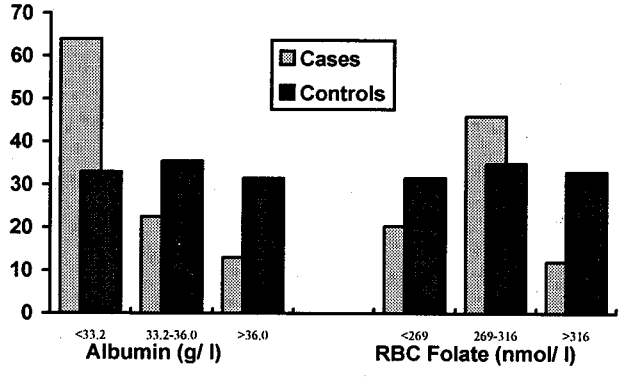
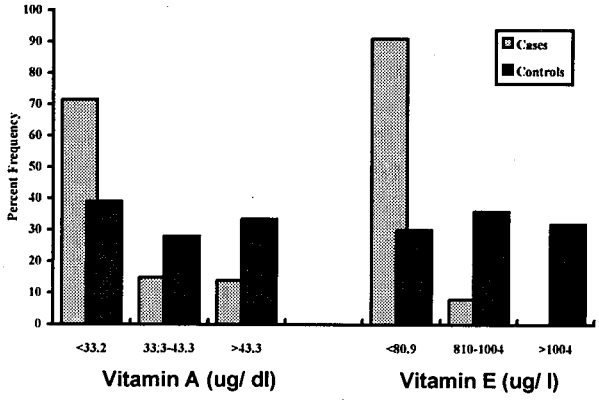


Figure 2. Tertile distribution of percent cases and controls for plasma vitamin A (p<0.01) and vitamin E (p< 0.001).



However, of the B-complex vitamins, red cell folate was significantly lower in cases (p <0.02). The status of other B complex vitamins, viz. thiamin and riboflavin were not affected.

Among fat soluble vitamins both vitamin A ($p < 0.005$) and vitamin E ($p < 0.001$) were significantly low. The tertile distribution indicated in Figure 2 reflects the same.

The two trace metals magnesium and zinc were significantly different from the controls with the former being higher while the latter was lower in cases, with all the case subjects falling in the first tertile (Figure 3). Serum copper level was not affected.

Figure 3. Tertile distribution of percent cases and controls for plasma magnesium ($p < 0.02$) and zinc ($p < 0.001$).

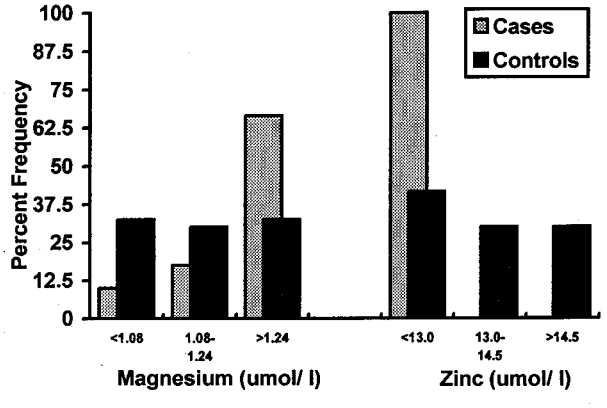


Table 3. Odds ratios (ORs) with 95% confidence intervals (CI) for oral cancer by tertile by nutrients in blood

Nutrient	OR	CI
Haemoglobin	1.00	
	2.57	(0.82-8.08)
	2.86	(0.92-8.90)
Albumin	1.00	
	1.44	(0.41-5.05)
	4.33	(1.36-13.82)
RBC Folates	1.00	
	3.92	(1.16-13.240)
	3.80	(1.11-13.030)
EGR	1.00	
	0.76	(0.27-2.15)
	1.45	(0.53-3.96)
ETK	1.00	
	1.90	(0.67-5.40)
	1.32	(0.48-3.59)
Vitamin A	1.00	
	1.38	(0.36-5.35)
	4.62	(1.47-14.52)
Iron	1.00	
	0.27	(0.08-0.95)
	0.87	(0.31-2.42)
Copper	1.00	
	0.42	(0.14-1.23)
	0.87	(0.31-2.43)
Magnesium*	1.00	
	1.73	(0.47-6.38)
	6.00	(1.77-20.31)

*The comparison in this is done with 1st tertile value.
No. of observations = 45

The odds ratios in Table 3 indicated that the risk was higher for low haemoglobin, albumin, folate and vitamin A; whereas the risk was higher for high magnesium levels. Plasma zinc and vitamin E values were not presented in the table as the populations of the two groups were well apart giving an infinite odds ratio.

Dietary assessment

Food Groups

The major food groups such as cereals, pulses, milk, vegetables and fruits were quantitated (Table 4). The vegetable intake green or otherwise was significantly low as compared to controls. In fact, the intake of both these food groups was only a third to half of that observed in controls.

When the frequencies of several food items (Table 5) were analysed, more frequent intake of other vegetables were associated with lower risk of oral cancer ($p < 0.01$), while the OR indicated a higher risk with lower consumption of vegetables and higher consumption of flesh and fried foods.

Nutrients

The nutrient intakes were computed as per the Nutritive Value of Indian Foods from the diet history. It was obvious that the cases and the controls were taking many fewer calories (Table 6)[29]. When all the nutrients were adjusted to the energy intake, the intake of carotene, riboflavin and magnesium were significantly higher in controls. The odds ratios show higher risk associated with low intakes of carotene, thiamin, riboflavin, folic acid, vitamin C, iron, magnesium and copper.

Table 4. Average intake (g) of food groups

Foods groups	Cases (16)	Controls (16)
1. Cereals	259±33.0	313±32.7
2. Pulses	23.4±4.34	24.8±4.56
3. Green leafy vegetables	9.09±0.97	26.29±8.08*
4. Other vegetables	50.1±11.79	106.4±19.45**
5. Milk & milk products	84.3±16.23	70.8±18.06
6. Flesh foods	15.4±6.08	10.3±3.18
7. Poultry products	8.1±6.12	7.5±2.39
8. Fruits	24.4±18.09	53.9±13.56
9. Oils/ fats	15.6±2.66	13.9±1.89

Figures in parenthesis indicate no. of observations.
All values are mean ± SE *P <0.05 **P <0.02

Discussion

Epidemiological observations throughout the world clearly demonstrate that environmental exposure to tobacco is an important factor in the aetiology of oral cancer[1]. Literary evidences document not only an association between tobacco and oral cancers but also highlight the risk modifying properties of certain specific food items such as vegetables and fruits and also of nutrients such as vitamin A, C and betacarotene[30-32]. Macro and micro nutrient deficiencies or imbalances have long been considered as probable causes or risk modifiers of cancer of the oral cavity[33]. Our study aimed to investigate the influence of dietary habits on the risk of tobacco induced oral and oropharyngeal cancers which were diagnosed within 2 months of the onset of signs and symptoms. It provided an opportunity to study the role of diet in the aetiology of oral

Table 5. Mean frequency of intake of food groups/ month with odds ratios (ORs) and 95% confidence intervals (CI) for oral cancer

Foods	Cases*	Controls*	OR[a]	CI
Cereals	75.2±7.8	86.3±3.8	0.43	
Pulses	26.8±5.3	31.9±6.6	1.00	
Green leafy vegetables	5.93±2.0	6.9±2.0	1.80	0.39-8.21
Other vegetables, roots & tubers	20.7±3.6	46.6±6.2**	∞	
Milk and milk products	9.4±3.5	6.9±3.8	0.51	
Animal foods	4.9±1.9	4.2±0.99	2.60	0.52-13.04
Fruits	7.0±2.2	7.5±2.2	1.29	
Fried foods	16.2±5.2	3.3±2.0	--	
Fish	0.75±0.28	0.19±0.13	0.18	
Tea/ coffee	61.9±9.6	37.5±7.5	0.20	
Fats and oils	0.6±0.24	0.5±0.31	0.21	
Spices	34.5±5.8	31.5±6.3	0.89	

No. of subjects in each group = 16. a: Median of the control taken as the cut-off point. *Mean±SE ** $p< 0.01$

Table 6. Calorie adjusted mean nutrient intake and odds ratio (ORs) with 95% confidence intervals (CI) for oral cancer

Nutrients	Cases[b]	Controls[b]	OR[a]	CI
Calories	1938.21±0.34	1984.27±0.34	--	--
Proteins (g)	49.85±0.30	47.20±0.28	0.45	--
Fat (g)	35.55±0.42	28.56±0.42	0.45	--
Calcium (mg)	545.00±0.57	596.90±0.45	1.29	
Carotene[a] (mg)	330.67±0.50	655.59±0.56*	3.00	0.67-13.40
Thiamin (mg)	0.68±0.43	0.81±0.35	2.20	0.52-9.30
Riboflavin (mg)	0.66±0.38	1.74±1.48*	4.33	0.88-21.30
Folic acid (µg)	103.75±0.40	128.65±0.36	4.33	0.88-21.30
Vitamin C (mg)	39.66±0.52	43.68±0.59	2.20	0.52-9.30
Iron (mg)	21.26±0.30	22.49±0.30	1.67	0.41-6.82
Magnesium (mg)	217.22±0.40	327.49±0.33**	5.57	1.13-27.52
Copper (mg)	3.05±0.43	3.91±0.32	4.33	0.88-21.31
Zinc (µg)	5308.8±0.51	5766.3±0.30	0.78	

No. of observations in each group = 16; a: negligible amount of vitamin A present (not included in carotene); b:Mean±SE; *$p< 0.05$; **$p< 0.01$

and oropharyngeal cancers. The tumour node metastasis (TNM) classification, suggest that most of them were diagnosed in the early stages of tumour development with or without the involvement of local lymph nodes with a few exceptions.

The findings of the present study either on the dietary intake prior to the onset of the disease or the nutrient profile at the onset, may be considered as indicators of natural sequence in the evolution of disease process, as not all nutrients are affected but only those that are aetiologically related.

The general nutritional status of the cases as reflected by body weight, BMI and albumin, appeared to be lower than the controls. We have earlier documented that protein energy malnourished individuals were at greater risk for developing cancers as they have a higher metabolic susceptibility to carcinogen such as polycyclic aromatic hydrocarbons[34-37].

The nutrient profiles estimated at the onset of the disease, indicated that vitamin A, E, zinc and folate-deficient subjects were susceptible to cancers. Several investigators have reported the protective effects offered by vitamins A and C rich foods[38-40]. The fact that in the present study the estimates of prior dietary intake indicated low intakes of betacarotene, riboflavin and vitamin C rich foods, favours the causal relationship of the nutrient deficiencies to the development of the disease process. The relative risk estimates, though of moderate magnitude, further reinforce the aetiological relationships as the subjects investigated were relatively homogeneous with respect to dietary intake.

It is interesting to note that dietary sources for betacarotene and folate are similar, namely vegetables, of which intake appears to be low. There is evidence to show that a precancerous condition has been associated with low folate intake[41]. Population based registries in India document a higher incidence of cervical cancers[42]. It is possible that folate in general may be involved in differentiation of epithelial cells as cancers at the above sites were all squamous cell carcinomas. Our observation on oesophageal cancer indicated low red cell folate levels. Infants in India are born with inadequate stores of folate and several other nutrients and continue to subsist on inadequate intakes of micro nutrients[42,43].

The sources of vitamin E in the Indian diet are vegetable oils and cereals. Though the intakes of these two items were not significantly different, the intakes in general, in both cases and controls were much less than the recommended dietary allowances. It is possible that in cases where other nutrient deficiencies exist, the

prooxidant and antioxidant balance is tilted towards adverse effect. Current research evidences support a strong preventive role for all antioxidants mentioned above in the causation of cancers at different sites. It was therefore not surprising to observe that vitamins A, C, E and betacarotene appeared to be protective in our series of cases. In the multistage carcinogenic process, which is complex, antioxidants appear to function as an inhibitor of promotional aspects of cancer[44].

In our earlier study on oesophageal cancers, results indicated a greater risk in individuals with low plasma zinc in addition to low vitamin A levels[45]. The discovery of the role of zinc in cancer is recent. Plasma zinc is known to decrease in several cancers[13]. Studies in China, Africa, Iran and Russia show a positive association between dietary zinc deficiency and higher incidence of oesophageal carcinomas[46-51]. Our study is one of the first to highlight an association between plasma zinc and oral cancer. The Indian diets which are cereal and pulse based are higher in phytates which can decrease absorption of zinc and contribute towards a zinc deficient state[52]. The intake of zinc particularly in the low income group is half of the recommended dietary allowance for Indians[29].

The experimental findings in relation to chemical carcinogenesis support our present observations of higher risk for zinc-deficient subjects particularly for nitrosamine induced cancers[53]. Zinc is known to have a significant effect on glutathione-S transferase and also on DNA repair mechanisms[54].

The relation of oral cancer with magnesium is intriguing. We have no satisfactory explanation for higher plasma magnesium levels in cases as compared to controls. The other non-nutrient dietary items examined were in line with the observations of Notani and Jayant on upper aerodigestive cancers wherein more frequent consumption of tea/ coffee, chillies and less frequent intake of fish appeared to increase the risk[55].

We are aware of the limitation in interpretation of our results. Familiarity with the hypothesis is a potent source of bias. Though the relationship between dietary constituents (nutrients and non nutrients) and cancer is complex, the consistent observation across wide population groups in different countries strongly support vitamins A, C and betacarotene as candidates for chemoprevention agents[56,57]. Our findings must be assessed in this context as the results are in agreement with previous epidemiological work in several countries[7,30,38].

Thus the micronutrients in the diet appear to play a pivotal role in reducing damage due to environmental exposures and probably act synergistically to enhance several protective mechanisms against carcinogenesis.

Acknowledgements

We thank Dr. Vinodini Reddy, Director, National Institute of Nutrition for her keen interest and valuable suggestions. We thank Mr KP Dalvi, Mr VK Goud, Mr PN Rao for their excellent technical assistance.

Diet and oral cancer - a case control study

MPR. Prasad, TP Krishna, S Pasricha, MA Quereshi, K Krishnaswamy

Asia Pacific Journal of Clinical Nutrition (1995) Volume 4, Number 2: 259-264

膳食與口腔癌症 —— 病例與對照的研究

摘要

除強烈的遺傳毒性致癌物以外，其它環境因素與癌症的預防和發生有關。本文在醫院內選用病例和對照，觀察了膳食在口腔和口咽癌症病因中的作用。作者從過去膳食史和生化營養狀況得到了過去食物進食和營養素的估計。結果指出，青菜水果進食少，連同β胡蘿白素、硫胺素、核黃素、葉酸、維生素C、鐵和銅進食低會增加癌症的危險。營養狀況的生物指標如血漿維生素A、E、紅細胞葉酸和血漿鋅濃度顯著減少會得到中等度癌症危險的估計。

這些發現與一些流行病學的觀察是一致的。微觀營養素的聯合作用可對抗煙草的致癌作用。而青菜和水果的保護作用，從病因和預防癌症的角度來說是有趣的。

References

1. World Health Organization, Control of oral cancer in developing countries-- a WHO Meeting. Bulletin of WHO Geneva 1984; 62: 817-830.
2. Annual Report, Population cancer registries-- New Delhi: Indian Council of Medical Research, 1989.
3. Micozzi MS. Foods, micronutrients, and reduction of human cancer. In: Moon TE, Micozzi MS, eds. Nutrition and cancer prevention. New York Marcel Dekker Inc, 1989: 213-242.
4. Lippman SM, Kessler JF, Meyskens FL Jr. Retinoids as preventive and therapeutic anticancer agents (Part I). Cancer Treat Rep 1987; 71: 391-405.

5. Lippman SM, Kessler JF, Meyskens FL Jr. Retinoids as preventive and therapeutic anticancer agents (Part II). Cancer Treat Rep 1987; 71: 493-515.
6. Tuyns AJ, Riboli E, Doornbos G. Nutrition and cancer of the oesophagus. In: Jossens JV, Hill MJ, Geboers J, eds. Diet and human carcinogenesis, Amsterdam Elsevier, 1985; 71-79.
7. Marshall J, Graham S, Mettlin C, Shedd D, Swanson M. Diet in the epidemiology of oral cancer. Nutr Cancer 1982; 3: 145-149.
8. Newberne PM, Schrager TF, Canner MW. Experimental evidence on the nutritional prevention of cancer. In: Moon TE, Micozzi MS, eds. Nutrition and cancer prevention. New York Marcel Dekker Inc, 1989: 33-82.
9. Hunter DJ, Willet WC. Human epidemiological evidence on the nutritional prevention of cancer. In: Moon TE, Micozzi MS, eds. Nutrition and cancer prevention. New York Marcel Dekker Inc, 1989: 83-100.
10. Steinmetz KA, Potter JD. Vegetables, fruit and cancer. I, Epidemiology. Cancer causes and control, 1991; 2: 325-327.
11. Ziegler RG. Vegetables, fruits and carotenoids and the risk of cancer. Am J Clin Nutr 1991; 53: 251s-259s.
12. Wattenberg L. Inhibitors of carcinogenesis. In: Griffen AC, Shaw CR, eds. Carcinogens: Identification and mechanisms of action. New York Raven Press 1979: 299-315.
13. Barch DH, Iannaccone PM. Role of zinc deficiency in carcinogenesis. In : Poirier LA, Newberne PM, Pariza MW, eds. Advances in experimental medicine and biology, New York Plenum Press 1986: 517-527.
14. Willet WC. Selenium, vit. E, fiber and the incidence of human cancer : An epidemiologic perspective. In: Poirier CA, Newberne PM, Pariza MW, eds. Advances in experimental medicine and biology. New York Plenum Press, 1986: 27-34.
15. National Nutrition Monitoring Bureau-- National Sample Survey Organisation linked survey report 1983-84, New Delhi: Indian Council of Medical Research.
16. Orr IM. Oral cancers in betel nut chewers in Travencore: its aetiology, pathology, and treatment. Lancet 1933; i: 575-580.
17. Dacie JV, Lewis SM. Practical haematology. Edinburgh Churchill Livingston 1991; 38-40.
18. Doumas BT, Biggs HG. Determination of serum albumin. In: Cooper GR, ed. Standard methods of clinical chemistry. New York Academic Press, 1972: 175-188.
19. Herbert V. The assay and nature of folic acid activity in human serum. J Clin Invest 1961; 40: 81-91.
20. Beutler E. Effect of flavin compounds on glutathione reductase activity in vivo and in vitro studies. J Clin Invest 1969; 48: 1957-1966.
21. Bayoumi RA, Rosalki SB. Evaluation of methods of coenzyme activation of erythrocyte enzymes for detection of deficiency of vitamins B1, B2, and B6. Clin Chem 1976; 22: 327-335
22. Bieri JG, Tolliver TJ, Catignani GL. Simultaneous determination of alpha-tocopherol and retinol in plasma or red cells by high pressure liquid chromatography. Am J Clin Nutr 1979; 32: 2143-2149.
23. Kayden HJ, Chow CK, Bjornson LK. Spectrophotometric method for determination of tocopherol in red blood cells. J Lipid Res 1973; 14: 533-540.
24. International committee for standardization in haematology. Proposed recommendations for measurement of serum iron in human blood. Br J Haem 1971; 20: 451-453.
25. Duncan L. Clinical analysis by aomic absorption spectroscopy. Springvale, Australia: Varian Techtron, 1976.
26. Snedecor GW. Statistical methods. Calcutta Oxford and I.B.H. 1967.
27. Willett W. Nutritional epidemiology. New York Oxford University Press, 1990.
28. Breslow NE, Day NE. Statistical methods in cancer research. Vol.1. The analysis of case control studies. I.A.R.C. Scientific Publication No.32, Lyon, France International Agency for Research on Cancer, 1980.
29. Gopalan C, Ramashastri BV, Balasubramanian SC. Recommended dietary allowances for Indians, In: Nutritive value of Indian foods. New Delhi Indian Council of Medical Research, 1989.
30. McLauglin JK, Gridley G, Block G. et al. Dietary factors in oral and pharyngeal cancer. J Natl Cancer Inst 1988; 80: 1237-1243.
31. Middleton B, Byers T, Marshall J, Graham S. Dietary vitamin A and cancer-- multi site case control study. Nutr Cancer 1986; 8: 107-116.
32. Winn DM, Zeigler RG, Pickle LW. Diet in the etiology of oral and pharyngeal cancer among women from the southern United States. Cancer Res 1984; 44: 1216-1222.
33. Wattenberg LW. Inhibition of neoplasia by minor dietary constituents. Cancer Res 1983; 43: 2448s-2453s.
34. Krishnaswamy K. Effect of malnutrition on drug metabolism and toxicity in humans. In: Hathcock JN, ed. Nutritional toxicology. New York Academic Press Inc, 1987; 105-113.
35. Krishnaswamy K. Malnutrition and chemical carcinogenesis. Proceedings of the Vth Asian Congress of Nutrition, Japan, 1987; 392-395.
36. Ramesh RP, Kalamegham R, Chary AK, Krishnaswamy K. Hepatic drug metabolising enzymes in undernourished men. Toxicol 1985; 37: 259-266.
37. Jagadeesan V, Krishnaswamy K. Effect of food nutrition on benzo(a)pyrene DNA binding in wistar rats. Toxicology 1989; 56: 223-226.
38. Rossing MA, Vaughan TL, McKnight B. Diet and pharyngeal cancer. Int J Cancer 1989; 44: 593-597.
39. Franceschi S, Bidoli E, Baron AE, Barra S, Talamini R, Sarraino D, La Vecchia C. Nutrition and cancer of the oral cavity and pharynx in north-east Italy. Int J Cancer 1991; 47: 20-25.
40. Franco EL, Kowalski LP, Oliviera BV, Curado MP, Pereira RN, Silva ME, Fava AS, Torloni H. Risk factors for oral cancer in Brazil: a case-control study. Int J Cancer 1989; 43: 992-1000.
41. Buckley DI, McPherson RS, North CQ, Becker TM. Dietary micronutrients and cervical dysplasia in southwestern American Indian women. Nutr. Cancer 1992; 17: 179-186.
42. Indian Council of Medical Research, National Cancer Registry, Annual Report 1987; New Delhi.
43. Iyengar L, Apte SV. Nutrient stores in human foetal livers. Br J Nutr 1972; 27: 313-317.
44. Weisburger JH. Nutritional approach to cancer prevention with emphasis on vitamins, antioxidants and carotenoids. Am J Clin Nutr 1991; 53: 226s-237s.
45. Prasad MPR, Krishna TP, Pasricha S, Quereshi MA, Krishnaswamy K. Oesophageal cancers and diet-- a case control study. Nutr Cancer 1992; 18: 85-93.
46. Burrel RJ, Roach WA, Shadwell A. Esophageal cancer in the Bantu of the Transkei associated with mineral deficiency in garden plants. JNCI 1966; 36: 201-209.
47. Warwick GP, Harington JS. Some aspects of the epidemiology and etiology of esophageal cancer with particular emphasis on the Transkei, South Africa. Adv Cancer Res 1973; 17: 81-229.
48. Akuman LV, Weinstein IB, Kaplan HS. et al. Specific cancers, cancer of oesophagus. In: Henny B, Kaplan S, Tsochitan PJ, eds. Cancer in China. New York Alan R Liss 1978.
49. Yang CS. Research on esophageal cancer in China: a review. Cancer Res 1980; 40: 2633-2644.
50. Van Rensburg SJ. Epidemiological and dietary evidence for a specific nutritional predisposition to esophageal cancer. JNCI 1981; 67: 243-251.
51. Mobarhan S, Dowlatshahi K, Diba YY. Hair zinc levels from a normal population of north east Iran with a high incidence of esophageal carcinoma (EC). Am J Clin Nutr 1980; 33: 940.
52. Nageswara Rao C, Narsinga Rao BS. Zinc balances in men and the zinc requirements in Indian adults. Nutr Rep Intl 1982; 26: 915-922.
53. Barch DH, Kuemmerle SC, Hollenberg PF, Iannaccone PM. Esophageal microsomal metabolism of N-nitrosomethyl benzyl-amine in the zinc-deficient rat. Cancer Res 1984; 44: 5629-5633.
54. Jagadeesan V, Oesch F. Effects of dietary zinc deficiency on the activity of enzymes associated with phase I and II of drug metabolism in Fischer-344 rats: activities of drug metabolising enzymes in zinc deficiency. Drug Nutr Interact 1988; 5: 403-413.
55. Notani PN, Jayant K. Role of diet in upper aerodigestive tract cancers. Nutr Cancer 1987; 10: 103-113.
56. Malone WF. Studies evaluating antioxidants and betacarotene as chemopreventives. Am J Clin Nutr 1991; 53: 305s-313s.
57. Singh VN, Gaby SK. Premalignant lesions: role of antioxidant vitamins and beta-carotene in risk reduction and prevention of malignant transformation. Am J Clin Nutr 1991; 53: 386s-390s.