NUTRITION AND MICRONUTRITION : HUMAN RISK FACTORS OR CANCER PREVENTION

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ACKNOWLEDGMENTS

This paper has been prepared in the framework of the Mitsuyoshi Nomura Foundation for Cancer and AIDS Research.

SUMMARY

Dietary factors have been estimated to be responsible for 30-40% of all cancer. Moreover, epidemilogical studies have revealed many correlations (coincidental, associated or precursor lesions) between the risk of cancer and the prevalence of other diseases. Thus, since all colorectal cancers arise in precursor areas of dysplasia, and since an adenoma is defined histologically as an area of dysplasia, adenomas are precursors of colorectal cancer.

In the case of colon cancer there is considerable evidence that a high proportion of large bowel cancers develop from a poliploïd precursion lesion, the adenoma. Study performed in France showed the role of diet in the occurrence of colorectal adenoma. The risk of colorectal adenomas decreasing linearly with increasing daily consumption of polysaccarides and natural sugar. In contrast sugar, added to food and drinks was observed to have the opposite effect.

In the oropharyngeal cancers the commonest precursor lesion is leukoplakia and the incidence of the cancer is strongly correlated with the intake of alcohol and smaking habit. It is also associated with a low intake of retinoids and carotenoids. In oesophagial cancer, the major histological type of cancer is squamous cell carcinoma (SCC) which accounted for more than 90% of all cases and the most widely recognized precursor of SCC is dysplasia in achalasia. In the large studies carried out in China, the major risk factors for dysplasia were low intakes of retinol, riboflavin, and zinc.

CHATENAY-MALABRY CEDEX, France

本稿は第12回微量栄養素研究会シンポジウムにおいて行なわれた特別講演の内容をとりまとめたものである。

In the aetiology of gastric cancer (GC) It is widely recognized that diet is the important factor. Reduction of nitrates (NO_3) to reactive nitrite (NO_2) formed through the action of nitrate-reducing bacteria in the saliva and an hypoacidic stomach can result in the subsequent formation of N-nitroso compounds (NOC) that can act as promoters during the later stage of carcinogenesis. Populations at high GC risk had a high NO_3 content in drinking water. Several case-control studies have shown remarkable consistency indicating that heavy use of salt would be compatible with a 50% increase in GC risk. Another factor that is known to have a large impact on GC is the dry heating (pyrolysis) of food rich in aminoacids and proteins which produces highly mutagenic aromatic amine compounds. Thus, the development of GC is multifactorial: excessive salt intake, low intake of fresh fruits and vegetables and *Helicobacter pylori* infection.

Finally, despite immense research efforts, the causes of breast cancers are still incompletely understood. Carcinogenesis consists of a series of steps which involve endogenous (hormones) as well, as exogenous (e. g. nutrition) factors similar to endometrial cancer in which the triad obesity-hypertension-diabetes and the unopposed action of oestrogens had been identified as potential risk factors.

In conclusion carcinogenesis often involves a multistage sequence of precancerous lesions, each step having its own set of causal agents. The role of diet and micronutrition in individual steps in the multistage carcinogenesis process in likely to provide the best clues to strategies for cancer prevention. Reduced fat intake, increased fiber intake, calcium intake and antioxidant compounds may be important not only in providing antioxidant substances but also in limiting the production of toxic oxidation compounds during food processing.

Since the oyster extract has been shown to be particularly rich in as well as Zn and in antioxidant compound, studies have been undertaken to show its effect on health promoting and as actively protective in cancer.

INTRODUCTION.

Problems raised by food intake will probably be in the next decade one of the main research target. It is related to various parameters such as age, sex, country, food habit, climate and health history of the patient. Although cancer mortality will be reduced by improved radiotherapy, chemotherapy or may be in the near future by gene therapy. Cancer will probably not be controlled by treatment, but rather by prevention (Wynder and Gori. 1977; Doll and Peto 1981). However, because the complexity of carcinogenesis process very little is known on cancer prevention and recently the only recommendations that could be made were: Eat more fruit and vegetables and avoid obesity. Whereas, to eat less fat or more fibre had to be suspended until the situation could be clarified (Benito et al. 1992).

To balance the deficiency or the excess of nutrients induced by food intake or by the pathology, micronutrients can be used by individuals. Among compounds that are widely used, fat is an important one.

The fatty acid composition which differs according to the origin of extraction can be saturated or unsaturated at different levels. According to their ratio it has been suggested to play a role in colon cancer frequency and in other pathologies (Giovannucci et al. 1994). Whether, this is due to changes induced in cell membrane composition or interfering with cellular metabolism is still not clear (Tapiero et al 1986; Tapiero and Zwingelstein 1989;. Dubois and Tapiero, 1992).

If we assume that cancer is the result of a multistage process in which the causes of the individual stage may differ. the control of precursor and its accociated lesions may help to prevent cancer.

Thus, a correlation can exist between the risk of cancer at a particular site and other diseases. This correlation can be coincidental or associated diseases.

Lesions can be precursor to cancers at different sites. In the case of oropharyngeal cancer which is the third commonest cancer site, the incidence of this type of cancer is strongly correlated with the intake of alcohol and with the smoking of tobacco (Johnson 1991; Garewal 1991;). It is also associated with poor nutrition particularly in the developing world. In most reports Squamous cell carcinoma has accounted for more than 90% of all cases. The most widely recognized precursor of squamous cell carcinoma is dysplasia in achalasia. In a very large studies it has been shown that the major risk factors for dysplasia were: low intakes of retinol, riboflavin and zinc (Thurnham et al., 1982. Others have suggested a causal role for tannins as chelating agents for zinc in the development of achalasia (Craddock, 1987). However, supplements of these were not able to reverse the development of these lesions (Munoz et al., 1985).

In the case of gastric cancer, high consumption of salty food such as pickled vegetables favors the development of *Helicobacter pylori* which has been shown to play an etiologic role in the development of gastric cancer. In a cross-sectional study of 634 men aged 40 to 49 years selected randomly from five areas with different rates of gastric cancer mortality, 474 Of 628 men evaluated were positive for lgG antibody against *H. pylori*. After logistic regression analysis adjusted for area, the results showed a significant association between frequent intake of pickled vegetables and prevalence of *H. pylori* antibody (Tsugane et al., 1994). Thus, risks for gastric cancer in relation to diet and other environmental factors are receiving renewed attention. Furthermore, new developments include th emerging relationship between *H. pylori* infection, increased risk of gastric cancer and positive results of chemoprevention trials in decreasing gastric risk with the use of β-carotene and vitamin E supplements. Factors that may enhance risk include consumption of nitrites, nitrates, alcohol, and highly salted, pickled, fermented or smoked foods. Other environmental factors which may promote cancer are *H. pylori* infection, inappropriate food storage, metal and cement dust exposure, and cigarette smoking. High intakes of fruits and vegetables or of antioxidants, such as β-carotene, vitamin E, and vitamin C may decrease risk (Hwang et al. 1994).

It was also proposed that the reduction of nitrate (NO_3) to highly reactive nitrite (NO_2) formed through the action of nitrate-reducing bacteria in the saliva and an hypoacidic stomach could result in the subsequent formation of N-nitroso compounds (NOC) which could act as promoters during the later

stages of carcinogenesis (Hartman 1983 ; Hill 1988 ; Forman 1991).

Similarly, high consumption of cooked meat can have a negative effect due to the presence of heterocyclic amines a group of potent carcinogens. The phenyllmidazo pyridine (PhIP) has been associated to the elevated risk of colon cancer. It is clear therefore that reduced intake of certain products or high intake of others can have a direct effect in the development of cancer lesions. However, if prevention can be achieved by appropriate diet, it has not been observed yet a cure of these lesions.

Nevertheless, the question that remains to be asked is what are the products that can play a role in Cancer prevention.

The role of micronutrients and vitamins as inhibitors of N-nitrosation in the aetiology of GC has also been widely studied and there is evidence that vegetables consumption does have a protective effect on GC risk. This effect has been demonstrated either in developing countries or high risk areas. A similar protective effect has also been shown for fruits (Foreman 1991; Graham et al., 1972; Hu et al., 1988; Risch et al., 1985).

In a modified Ames/Salmonella mutagenicity test, vegetables or fruits have been demonstrated to be antimutagenic at different levels following induction by the amino-methyl quinoline.

These antimutagenic activities may be associated to the peroxidase activity found to be present in some vegetables (broccoli, cauliflower, green beans and tomatoes). The interest in dietary fiber is based on the observation that several diseases present in western countries: diabetes, hypertension, coronary heart disease, hyperlipidemia, large bowel diseases and cancer, have infrequent occurrence in developing countries. The consumption of unrefined vegetable rich in fiber is very high in developing countries and low in the western world.

Free radicals are responsible for DNA and membrane damages (Table 1). To reduce the negative effects of free radicals formed by superoxydes ions and NOC generated by food intake or anticancer drugs (Crescimanno et al 1991), micronutrients have been proposed in the chemopreventive strategy and as adjuvent in the treatment of some pathologies.

Table 1. Cell protection against free radicals

Superoxide Anions ($O_2^{\cdot -}$)	transformed into H_2O_2 by the SUPEROXIDE DISMUTASES (SOD's)
	Mn-SOD localised in mitochondria
	Cu/Zn-SOD localised in cytosol
H_2O_2	Transformed into H_2O and O_2 by :
	catalases
	Selenium dependent glutathion peroxidases (GPXs)
Molecular Antioxidants	(liposoluble) Vitamin E, Carotenes
	(hydrosoluble) Glutathione (G-SH), Vitamin C, Taurine

Thus supplementation of vitamin C an α-tocopherol resulted in a significant reduction in the mutagenic compounds excreted with faeces.

This suggest that antioxidant in the diet may have a role in lowering the body's exposure to endogenously formed mutagens.

Protection from free radicals can be achieved by antioxidant cocktails such as vitamin A, preformed retinol or carotenoids, vitamin E or cofactors of vitamin C. However the effect have provided contradictory results in protection from oxidative damage.

Another compound used is glutathione a tripeptide (L-γ-glutamyl-L-cysteinyl-glycine) may function as an anticarcinogen by acting as antioxidant or by binding with cellular mutagens (Schisselbauer et al., 1989; Flagg et al. 1994). Dietary glutathione intake in humans can increase the plasma glutathione levels, fruits and vegetables were found to contribute over 50% of usual dietary glutathione intake, whereas meats contribute to less than 25%. Moreover, another important component is the nonprotein amino acid, taurine a 2-aminoethanesulphonic acid that can act as detoxifier, membrane stabilizer and antioxidant. This compound has been found to be enriched in the oyster extracts (Nippon Clinic, Kyoto, Japan). However, it remains to determine whether the oyster extract play an effective role in the prevention against the potentially carcinogenic compounds.

RESULTS

At the cell level, Chenges in phospholipid composition of the cell membrane is associated with changes in membrane fluidity. Changes in lipid composition and consequently changes in membrane fluidity can be an important parameter in not only cell differentiation and transformation but also in the resistance to anticancer drugs (Tapiero et al., 1986; Tapiero & Zwingelstein 1989; Dubois and Tapiero 1992). However, whether or not restoring the physiological lipid composition of the cell membrane in the organism will circumvent the resistance to anticancer drugs remains to be shown.

Table 2. CONTENTS OF FATTY ACIDS

Oil	Saturated fatty acid ($H_3C-CH_{2(n)}-CH_2-COOH$)	Oleic acid (mono-unsaturated)	Linoleic acid (di-unsaturated)	α-Linolenic acid (tri-unsaturated)
Palm	51.7	39.3	8.8	0.2
Olive	14.5	73.0	11.7	0.8
Colza	7.0	64.1	20.9	8.0
Arachide (Africa)	18.8	59.8	21.3	0.1
Arachide (USA)		42.9	36.5	
Soja	14.9	25.3	51.0	6.8
Corn	13.6	29.4	55.9	1.1
Walnut	7.8	13.9	65.1	13.2
Sunflower	12.5	21.2	66.1	0.2
Grape's seed	11.4	16.1	72.1	0.4

Glutathione may function as an anticarcinogen by acting as an antioxidant or by binding with cellular mutagens (Table 3). Orally administered glutathione increases plasma glutathione levels, and plasma glutathione is also synthesized in the liver (Table 4). Daily glutathione intake ranged from 13.0 to 109.9mg (mean 34.8mg). Fruits and vegetables were found to contribute over 50% of usual dietary glutathione intake, whereas meats contributed less than 25%. Small negative correlations were observed between dietary and plasma glutathione and, although they were usually not statistically significant, they were generally consistent by different time periods of dietary intake assessment. Adjustment for sex, age, caloric intake, and dietary intake of the sulfur-containing amino acids methionine and cystine did not alter the observed associations. The correlations appeared to be modified, however, by serum vitamin C concentration, with little or no association between dietary and plasma glutathione among those with lower levels of serum vitamin C and stronger negative correlations among those with higher serum vitamin C levels. These findings indicate that factors regulating plasma glutathione concentration are complex and not simply related to dietary glutathione intake or supply of precursor amino acids (Flagg et al. 1994).

The antimutagenic potencies of the juices of fruits and vegetables were investigated by (Edenharder et al 1994) with respect to the mutagenic activities induced by 2-amino-3-methyl [4,5-f] quinoline (IQ), and in part by 2-amino-3,4-dimethylimidazo [4,5-f] quinol (MelQ) or 2-amino-3,8-dimethylimidazo [4,5-f] quinoxaline (MelQx) in *Salmonella typhimurium* TA98 and TA100. With IQ, weak to strong anti-

Table 3. Simplified pathways for involvement of Glutathione and Glutathione S-transferase isoenzymes in Xenobiotic metabolism

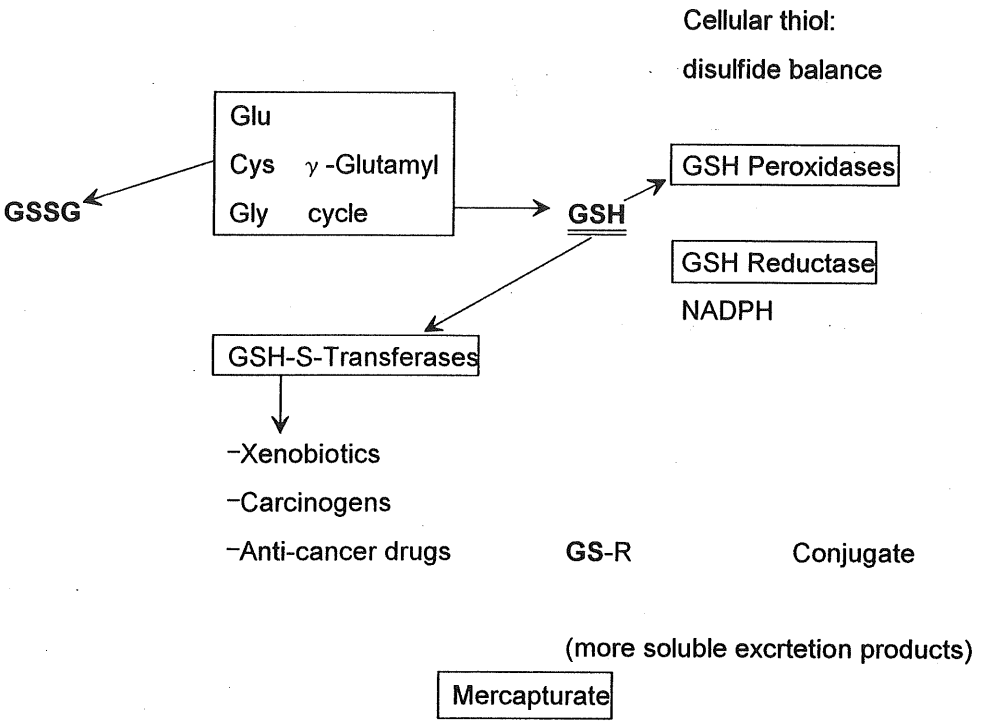

Table 4. Tissue Glutathione (GSH) levels Tissue GSH (μmol/g)

Tissue	
Brain	2.08
Heart	1.35
Lung	1.52
Spleen	3.43
Liver	7.68
Pancreas	1.78
Kidney	4.13
Small Intestine mucosa	2.94
Colon mucosa	2.11
Skeletal muscle	0.78
Plasma (μM)	28.4

mutagenic activities were found in 68% of the fruits and 73% of the vegetables that were tested (Table 5). In fruits, strong antimutagenic activities were detected in bananas, blackberries, blueberries, sweet and sour cherries, blackcurrants and redcurrants, pineapple and watermelon. Moderate antimutagenic activities were detected in greengage, kiwi, mangos, honeydew melons and plums. Weak antimutagenic activites were detected in apple, apricot, mirabelle, pears, peaches and strawberries, whereas white and red grapes and raspberries were inactive, and gooseberries and citrus fruits in general possessed marginal or no antimutagenic activities. In vegetables, strong to moderate antimutagenic activities were found for all cruciferous vegetables, except Chinese cabbage, which had only weak antimutagenic activity. Other vegetables with strong antimutagenic activities were beets, chives, horseradish, onions, rhubarb and spinach. Moderate antimutagenic activities were found with green beans and tomatoes, weak activities in eggplant, garden cress, many lettuces, leeks, mangold, cucumber, pumpkin, radish and summer squash. Asparagus, carrots, fennel leaves, parsley, green peppers and radishes were inactive. When fruit and vegetable juices were heated, a considerable reduction of antimutagenic potencies was seen with apple, apricot, kiwi, pineapple, beets, cabbage (Chinese, Savoy, red and white), cauliflower, leafy lettuce, cucumber, onions, radish and rhubarb. Antimutagenic factors in blackberries, blueberries, sweet and sour cherries, honeydew melons, mirabelle, plums, strawberries, Brussels sprouts, chicory greens, eggplant, garden cress, mangold, pumpkin, lamb's lettuce and spinach were, however, remarkably heat stable. Antimutagenic potencies in bananas, blackcurrants and redcurrants, greengages, gooseberries, mangos, watermelon, green beans, kohlrabi, horseradish, tomatoes and chives were partially reduced. Antimutagenic activities in the juices of eight apple cultivars were moderate in two, weak in four, and marginal or absent in two. No major differences, however, were detected in five batches of oranges and three batches each of grapefruits, asparagus, green beans, broccoli, cauliflower, spinach and tomatoes. No (or only minor) differences were seen between IQ, MeIQ and MeIQx and tester strains TA98 and TA100. Pineapple and celeriac juices inhibited the enzymatic system responsible for the activation of IQ, but had no de-

Table 5. ANTIMUTAGENIC ACTIVITY induced by 2-amino-3-methyl [4, 5-f] quinoline (IQ)

	Strong	Moderate	weak	inactive
Vegetables	cruciferous	green beans	eggplant	fennel leaves
	beets	tomatoes	lettuce	green peppers
	horseradish		cucumber	parsley
	onions		radish	asparagus
	rhubarb		pumpkin	carrots
	spinach			
Fruits	bananas	kiwi	apple	grapes
	blueberries	mangos	apricot	raspberries
	cherries	honeydew	pears	
	pineapple	melons	peaches	
	watermelon	plums	strawberries	

Table 6. ANTIMUTAGENIC ACTIVITY induced by 2-amino-3-methyl [4, 5-f] quinoline (IQ)

	Heat Labile	Heat Stable
Vegetables	beets	eggplant
	cauliflower	garden cress
	cabbage	spinach
	onions	
	lettuce	
	spinach	
	radish	
	rhubarb	
Fruits	apple	blueberries
	apricot	cherries
	kiwi	melons
	pineapple	plums
		strawberries

smutagenic activity. Peroxidase activity found to be present in broccoli, cauliflower, green beans and tomatoes may contribute to antimutagenic activities in these vegetables.

The determinants of plasma concentrations of α-tocopherol, β-carotene, retinol, and cholesterol fractions in a randomly selected workers found that they could explain 35% of the variability in plasma beta-carotene, 73% of the variability in α-tocopherol, 36% of the variability in retinol, and 19% of the variability in cholesterol. Plasma β-carotene levels appeared to be affected by the use of supplements that did not contain carotene, indicating a β-carotene sparing capability of other agents contained in these preparations. Plasma α-tocopherol levels were not similarly affected. These results compare favorably with those from studies that used more intensive dietary assessment techniques as the comparison

Table 7. Antioxydant Preparations

	β-Carotens* (mg)	Vitamin C (mg)	Vitamin E (mg)	Se (μg)
NEEDS (ADULTS)	800-1000	60-100	10-15	50-100
FINLAND STUDY [1]	9	90	60	100 (organic)
WALFOR FORMULAE [2]	0	1600	600	160
BETASELEN [3]	12	200	200	100
FORMULAE 144, USA	15	500	500	50

[*] 6mg of β-Carotens=1000 retinol equivalent=1000 μg vitamin A
[1] +15mg Zn (gluconate) +800mg Se (mineral) +400mg vitamin E
[2] +300mg flavonoids+300mg cystein+120mg methionin+250 μg Butylhydroxytoluene
[3] +5mg Zn

criterion (Hebert et al. 1994).

In conclusion, the prevalent view of human carcinogenesis postulates a multistep process the relationship between diet and cancer risk is suffering from a lack of clarity. *H. pylori* infection and low intake of ascorbic acid are strongly associated with the precancerous stage of intestinal metaplasia and dysplasia (Reed 1992). Nevertheless, diet can represent a fundamental tool for cancer prevention. Various sets of dietary recommendations have been issued to characterize the type of nutrition whis is associated with a lower risk for cancer disease. Although the relationship between diet and cancer is a very controversial, there is a strong positive correlation between cancer mortality rates and consumption of fat, animal proteins and refined sugars, while the correlation with complex carbohydrates tends to be negative. Therefore there is a need to prevent or correct obesity reducing daily energy intake thus improving risk factors which are often associated with overweight such as hyperlipidemia, hypertension and diabetes. Dietary recommendations emphasize the importance of vegetable foods as partial substitutes for foods of animal origin. Vegetables products are rich in water soluble fiber which improve glucose tolerance and prevents carbohydrates induced hypertriglyceridemia. Another recommendation given in dietary is to reduce salt and alcohol intake. We await the outcome of future studies which hopefully will confirm that minimising risk factors and to use micronutrients should lead to a further reduction in the incidence of cancer.

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