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Nutritional Factors in Carcinogenesis

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Abstract

There have been varying estimates of the role of nutritional as opposed to other contributors to carcinogenesis. Several considerations probably account for the different estimates:

1. genetic overestimates because of fetal and early life rearing practices and the nutritional modulation of genetic expression
2. errors in food intake methodology
3. the limitations of nutrient-carcinogenesis hypotheses ie. models which are too naive and do not allow for non-nutrients in food, food patterns and the overall "package" which is food culture.
4. indirect pathways connecting nutrition and cancer such as that via immunosurveillance

Examples of cancers where rapid change in nutritional thinking is underway are breast, prostatic, colorectal and pancreatic.

With breast cancer, weakly oestrogenic compounds from food may be comparable to tamoxifen. Changing food culture away from that rich in phyto-oestrogens may increase the risk of prostatic cancer in men as well. Colorectal cancer incidence has continued at high rates in urbanized society despite an awareness of dietary contribution comparable to the knowledge of diet and coronary heart disease - is the analysis sufficiently stratified for large bowel site or nutritionally sophisticated enough to allow for aggregate food pattern effects? Pancreatic cancer on the rise presents questions about unidentified changes continuing in the diets of industrialized societies, possibly from an early age, and even during infant feeding.

Nutritional surveillance with mathematical modelling of food intake at a more sophisticated level will be required to understand present food-cancer relationships, and those which may emerge with newer food technologies, especially those related to designer foods. *(Thai Cancer Journal 1993; 19:67-74).*

Energy Intake

The role of energy intake in carcinogenesis is a vexed one[1,2]. There has been a popularised view, derivative of mainly rodent experiments, which has argued that energy restriction may decrease the cancer risk and increase longevity[2-4]. Most of these studies are flawed insofar as extrapolation to humans are concerned because either they are conducted from early life with excessive early mortality, or they do not account for energy expenditure and therefore energy balance, reflected in body fatness and/or its distri-

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bution[5]. Where the full energy equation is available, increased energy throughput (eg. higher energy intakes with no increase in body fatness) has been associated with decreased cancer risk and/or increased life expectancy[6,7]. Increased energy intake (and possibly its frequency, according to Potter[8-10] has in its own right been associated with increased cancer risk at several sites[1,11]. Again, as will be discussed elsewhere in this paper, the quality of the extra food intake seems important[5,12].

Macronutrient

Much of the focus of nutrition and cancer since the late 1970s, when industrialized nations began to develop Dietary Guidelines, to reduce the burden of chronic non-communicable disease, has been the macronutrients in food. Increasing incidences of colorectal cancer and breast cancer, in particular, were associated with relatively high fat intakes and low dietary fibre intakes[13]. Whether these relationships were causal or not was another issue, but the overall dietary and cancer patterns were impressively associated in *trans-national* and *immigration studies*. Even some of the variance of the principal cause of death from cancer in men, lung cancer, was found to be explained for a given level of cigarette smoking by plant food intake[13]. Increased plant food intake, expressed in terms of dietary fibre, was predictive of reduced cancer mortality in the Zutphen (Netherlands) part of the 7 countries study, originally designed to examine the dietary contributions to coronary heart disease[5].

A number of cross-cultural studies examined each of the macronutrients

- protein, its source and quality
- carbohydrate, its refinement and monomeric components (glucose, fructose, galatose)
- fat, its quality
- dietary fibre, its sources and chemistry
- alcohol and the type of beverage from which it comes

and, later, resistant starch, to consider how macronutrients might contribute to carcinogenesis. Both amount and percentage contribution to energy intake were considered. The general consensus which emerged is shown in Table 1.

Long-term observational studies to examine the macronutrient-cancer hypotheses have still been few, and then with a particular food culture, so that the full range of the human diet and its possible macronutrient contribution to carcinogenesis has not been easily appreciated. For example a major US nutrition observational study has not confirmed a role for dietary fat intake on breast cancer in US women, but fat intakes as a percentage of energy intake have only been studied close to 32 per cent[14-19]. Observation in mainland China suggest that it may be necessary to have this energy percentage less than 20 (or 25) per cent to see the effect of dietary fat[20].

For colorectal cancer, the Australian Poly Prevention Project Study has shown no detectable effect on adenoma incidence at 2 years with fat intake <25 per cent, with or without wheat bran supplementation (25 g/day) or beta-carotene supplementation (20 mg/day)[21]. Other studies are awaited. This study will have had more of a likelihood of detecting effects on promotion than on initiation.

Further studies of macronutrient intervention are awaited.

There is also interest in whether genetically disposed individuals are more susceptible to a particular nutrient intake and this may apply in almost any cancer - colorectal, breast or whatever. Of particular interest has been the possibility that some women have a mild form of galactosaemia which puts them at risk of ovarian cancer with regular milk ingestion[22,23].

Experimental animal work has allowed some of the macronutrient - carcinogenesis hypotheses to be further evaluated and validated. The nutritional metabolism basis of cancer has thus been better understood. For example, omega-6 fatty acids have been found detrimental whilst omega-3 fatty acids and monounsaturated fatty

Table 1 Nutritional risk factors for breast, colorectal, prostate and ovarian cancers.

	Protective	Detrimental
Nutritional risk factors for breast cancer		
1. Energy balance	+	
Body fat		
(Total fat and distribution)		
- Premenopausal		
- Post-menopausal		+
Physical activity	+	
2. Fat intake *(> 20% energy)*		+
3. Fat quality *(↑ Omega-6)*		+
4. Alcohol *(> 5 g/day)*		+
5. Soya products	+	
(increase traditional products)		
?Phytoestrogens		
6. Meat intake		+
7. Reproductive life span	?	?
Its nutritional determinants		
8. Vitamin A from food	+	
Nutritional risk factors for colorectal cancer		
Fruit and vegetable	++	
Wheat bran/	+ (high fat diet)	
Cereal fibre		+ (low fat diet)
Diary components		
Ca	+	
Vitamin D	+	
Whey proteins	+	
Alcohol		+
Fat		+
Nutritional risk factors for prostate cancer		
Vegetables	+	
- Green leafy and yellow	+	
- Soya	?	
Fat intake		?+
Body mass		+
? Muscle mass		+
? Physical activity		+
Cadmium		?+
Nutritional risk factors for ovarian cancer		
Galactose		+
"More common in women who drink milk every day"		
-? genetic predisposition through galactosaemia		
? Obesity		?+
Fruits and vegetables	+	
Fat intake		+

acids from olive oil protective in experimental models of mammary and colonic tumors[24]. It has been difficult to reach this level of analysis with human studies so far. Animal versuses plant protein has likewise been examined with mixed results (see below).

The detailed metabolic analysis of single (or even general) macronutrient experiments sometimes "misses the wood for the trees". In a total diet macronutrients may simply serve as surrogates for other dietary factors, or food or meal patterns. Potter and colleagues[9,10,25,26] have provided evidence in cross-cultural studies that quantity and frequency of food ingestion (even of cereal fibre) may be of increased risk for colonic cancer[26] - although whether this applies with all dietary patterns and at different phases of physical activity (or energy throughput) need further clarification. In the case of coronary heart disease (CHD) risk factors, low fat snacking seems favourable[27] and needs reconciliation with large bowel cancer studies (although the two industrialized society disease profiles can operate independently of each other, Table 2).

Micronutrient

There has been a long-standing interest in the potential for micronutrient deficiency to allow the development of certain cancers, and for the rectification of such deficiencies to be preventive (Table 3)[28]. A separate consideration has been whether pharmacological doses of certain vitamins, like those with antioxidant properties might be protective[29] - if they were, then some would argue for a revision of the present Recommended Dietary Allowances (RDAs) (or RDIs, Recommended Dietary Intakes). This is a vexed point, but as yet there is no clear evidence that vitamin or element intakes beyond those with in reach of the human diet may have any special role. The one exception might be the water soluble B-vitamin folacin for dysplastic conditions of cervix or large bowel[30-35] or of large bowel adenomata[36].

It is, of course, possible that as yet undetermined or presently emerging mechanisms of micronutrient action might provide a more rational basis for recommendations. For example, the role of Vitamin B-6, Vitamin D, and selenium in immune function may be of significance in tumour formation found in states of immunodeficiency (aging, in HIV positive individuals, and in immunosuppressed transplant patients).

Intervention studies are now providing more confidence in the micronutrient-cancer field (Table 4). The most notably relevant study in this area in recent times is the *Linxian,* Henan Province, China study of oesophageal and gastric cardia cancer, and of oesophageal dysplasia[37]. A combination of beta-carotene, Vitamin E and selenium, in this deficient area, reduced risk,

Table 2 Diet-cancer patterns

Diet & lifestyle	Oriental	Mediterranean	Other occidental
Cancer	Gastric	Gastric	Breast
	Primary Hepatic		Colorectal
	Oral		Pancreas
	Naso-pharyngeal		Endometrium
	Oesophagus		Ovary
			Prostate
Non-cancer chronic Non-communicable disease	CVD	Obesity	Obesity
		Diabetes	CHD
			CVD
			Diabetes

whilst this was almost achieved for a combination of riboflavin and niacin as well. Doses, over 5-1/4 years, were 1-2 fold the RDAs - dose-response data are not available.

The *Australian Poly Prevention Project* on the other hand, a 2 year (and then further 2 years) 2x2x2 factorial designed study of beta-carotene (20 mg/day) versus placebo in conjunction with low fat and/or increased wheat bran, provided no evidence for protection by beta-carotene against the incidence of recurrent adenomas[38,39]. Further analysis of background carotenoid intakes and their effects is underway.

Table 3 Nutrition and cancer micronutrients pathogenesis (protection)

	Cancer site
Vitamins-water soluble	
B-2	Oesophageal
Folacin	Cervical dysplasia
	Colorectal
	- dysplasia
	- adenoma
Vitamin C	? Various
Vitamin-fat soluble	
Vitamin A *(preferred)*	Skin
	Breast
	Lung
Beta-carotene	Oesophageal
	Gastric cardia
	? Colorectal
	Lung
Vitamin D	Cell differentiation
Vitamin E (and tocopherol)	Oral
	Pharyngeal
	Oesophageal
	Gastric cardia
Elements	
Major	
Calcium	Colonic
Minor	
Selenium	Oesophageal
	Gastric cardia
Zinc	? Oesophageal

Non-nutrients in food

Food chemistry has been oversimplified for the purposes of consideration of nutrition-chronic disease pathogenesis. There are hundred of compounds, other than macro-and micronutrients, with potential biological effects in food, such as those that provide food colour, arena and taste, aroma and taste, as well as its keeping properties (eg. antioxidants). Some of these that may provide protection against cancer at different stages are shown in Table 5.

Phytoestrogen

Tamoxifen is an effective management and possibly protection agent against breast cancer in oestrogen sensitive tumours, because of its anti-oestrogenicity at this site. But it is weakly oestrogenic at other sites like vagina[40] and bone[41]. It follows that phytoestrogens from foods like soya products may be protective against breast cancer, as appears to the case in studies of Singaporean Chinese women by Lee et al[42].

Salicylate

Salicylate, possibly even more so than acetylsalicylic acid (aspirin), through effects on membrane properties may affect cancer expres-

Table 4 Intervention trials

	Intervention	Study
Breast cancer	Tamoxifen	
Prostatic cancer	Under consideration	Kolonel and Nomura
Colorectal cancer		
- Pre cancerous	Fat	APPP
	Fibre *(micronutrient, fruit and vegetable)*	NCI
Oesophageal/Gastric cardia	Micronutrients	Lin Xiang

Table 5 Food non-nutrients of putative significance in cancer prevention

Component	Relevant cancer
Salicylates	Gut tumours
	- *Oesophagus*
	- *Gastric*
	- *Colorectal*
Phytoestrogen	Breast
	?Prostate
Glutathione/whey proteins	Colon
Non pro-vitamin A carotenoids	Various
Flavonoids	Various
Tannins	Skin
	Lung
Curcumin (in tumeric)	Various
Enzyme-inducers *(eg. in broccoli)*	Colon
Resistant starch	Colon

sion. Aspirin itself has been shown to be associated with significantly less GI (gastrointestinal) cancer at several sites[43]. Salicylates are present principally on fruits[44] and may partly explain the protection of these foods against certain types of cancer.

The antioxidant effects of non-vitamin A precursor carotenoids (eg. lycopene, biotin, cryptoxanthin, zeaxanthin) and flavonoids (eg. quercetin) may be cancer protective[45].

Food pattern

Comment has already been made on the relative merits of snacking in relation to neoplasia and macrovascular disease[25].

Breakfast as a time of day to achieve a significant fraction of the day's nutrient needs is receiving more attention[46]. It has also been targeted by breakfast cereal manufacturers as a "cancer-protective meal" or episode of eating.

Better ways of describing the human diet mathematically are required if preferred eating patterns in respect of neoplastic disease and all-cause mortality are to be accorded confidence.

Moreover, what is often left unsaid or studied in food pattern-health relationships is the social role of food. Food can be a social facilitate and, in term, social activity a predictor of health[47]. Certainly, social activity can encourage the consumption of food variety and a correspondingly healthful dietary pattern[48]. How these considerations affect the nutrition - cancer relationship is worthy of investigation.

Food variety

Until recently, the advocacy for food variety has been something of a nutritional cliché, although espoused in all Dietary Guidelines. It ensures essential nutrient adequacy if wide enough, and discourages ingestion of excessive quantities of endurable food components[49].

There is now evidence that food variety, expressed as a Food Diversity score in the NHANES I[50] study is powerfully predictive of all-cause mortality, more so far men than women[12]. It will therefore be of value in future cancer studies as one way to achieve a mathematical descriptor of the human diet[49].

Table 6a Immunomodulators in food and cancer

A. Macronutrient
- eg. Alcohol
- Fat (n-3/n-6)
- Amino acids (glutamine)

B. Micronutrient
- eg. B-6
- Vitamin D
- Zinc
- Selenium

C. Non-nutrient
- eg. Glutathione
- Flavonoids

Table 6b Immunosuppressed people at risk of cancer and where nutritionally reversible components may be in evidence

1. The aged
2. HIV positive individual
3. Transplant patients

Cancer, immunodeficiency and nutrition

Neoplastic disease is more common in association with immunodeficiency in the following settings:

(1) Aging

(2) HIV positivity

(3) Transplantation with immunosuppression

There are prospects for the nutritional immunomodulation of these situations (Tables 6a and 6b)[51].

Designer or functional foods

Food technology proceeds apace and views with interest the newer developments in nutrition and cancer science. Novel and analogue foods will undoubtedly emerge which incorporate this new science. They will require recognition in the market-place, distinguished from *"traditional foods"* and, where health claims are made, designated as *"medical foods"*. There will be risks and their long term evaluation will require a new "food toxicology"[52].

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