

REVIEW ARTICLE

Nutritional factors in carcinogenesis

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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 foetal 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 foods 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.

Energy intake

The role of energy intake in carcinogenesis is a vexed one^{1,90}. There has been a popularized view, derivative of mainly rodent experiments, which has argued that energy restriction may decrease the cancer risk and increase longevity^{87,88,90}. 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 distribution⁵⁶. Where the full energy equation is available, increased energy throughput (ie higher energy intakes with no increase in body fatness) has been associated with decreased cancer risk and/or increased life expectancy^{29,6,0}. Increased energy intake (and possibly its frequency, according to Potter^{86,93,94}) has in its own right been associated with increased cancer risk at several sites¹². Again, as will be discussed elsewhere in this paper, the quality of the extra food intake seems important^{10,56}.

Macronutrients

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 intakes⁴¹. Whether these relationships were causal or not was another issue, but the overall dietary and cancer patterns were impressively associated in *trans-rational* 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 intake⁴¹. Increased plant food intake, expressed in terms of dietary fibre, was predictive of reduced cancer mortality in the Zutphen (Netherlands) part of the seven countries study, originally designed to examine the dietary contributions to coronary heart disease⁵⁶.

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

- protein, its source and quality
- carbohydrate, its refinement and monomeric components (glucose, fructose, galactose)
- fat and its quality
- dietary fibre, its sources and chemistry

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• 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 at intakes as a percent-

age of energy intake have only been studied close to 32%¹²⁹⁻¹³⁴. Observations in mainland China suggest that it may be necessary to have this energy percentage less than 20 (or 25)% to see the effect of dietary fat¹³⁵.

For colorectal cancer, the Australian Polyp Prevention Project Study has shown no detectable effect on adenoma incidence at 2 years with fat intake <25%, with or without wheat bran supplementation (25 g/day) or beta-carotene supplementation (20 mg/day)⁷². 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^{1,105}.

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 acids from olive oil protective in experimental models of mammary and colonic tumours¹⁰⁴. It has been difficult to reach this level of analysis with human studies so far. Animal versus plant protein has likewise been examined with mixed results⁹⁷.

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 colleagues⁹²⁻⁹⁵ 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 cancer⁹⁵ – although whether this applies with all dietary patterns and at different phases of physical activity (or energy throughout) needs further clarification. In the case of coronary heart disease (CHD) risk factors, low fat snacking seems favourable⁴⁹ and needs reconciliation with large bowel cancer studies (although the two industrialized society disease profiles can operate independently of each other, see Table 2).

Table 1

Nutritional risk factors for breast cancer		
	Protective	Detrimental
1. Energy balance	+	
• Body fat (total fat and distribution)		
– Premenopausal		+
– Postmenopausal		
• 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		
	Protective	Detrimental
Fruit and vegetable	++	
Wheat bran/ cereal fibre	+(high fat diet)	+(low fat diet)
Dairy components		
Ca	+	
Vitamin D	+	
Whey proteins	+	
Alcohol		+
Fat		+
Nutritional risk factors for pancreatic cancer		
	Protective	Detrimental
Energy		+(47)
Caffeine		?
Cholesterol		+(47)
Trypsin inhibition		+
Alcohol		?
Build (larger)		+(79)
Fish Oil	?+	+
Protein (and high fat)		+
Nutritional risk factors for prostate cancer		
	Protective	Detrimental
Vegetables	+	
– Green leafy and yellow	+	
– Soya	?	
Fat intake		?+
Body mass		+
? Muscle mass		+
? Physical activity		+
Cadmium		?+
Nutritional risk factors for ovarian cancer		
	Protective	Detrimental
Galactose 'More common in women who drink milk every day' – ? genetic predisposition through galactosaemia		+
? Obesity		?+
Fruit and vegetables	+	
Fat intake		+

Table 2 Diet – cancer patterns.

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

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 (<i>preferred</i>)	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

Micronutrients

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)⁹. A separate consideration has been whether pharmacological doses of certain vitamins, like those with antioxidant properties might be protective^{117,121} – 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^{6,7,15,16,26,61} or of large bowel adenomata³³.

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 B₆, Vitamin D, and selenium in immune function may be of significance in tumour formation found in states of immunodeficiency (ageing, 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 dysplasia⁶⁷. A combination of beta-carotene, Vitamin E and selenium, in this deficient area, reduced risk, whilst this was almost achieved for a combination of riboflavin

Table 4 Intervention trials.

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

and niacin as well. Doses, over 5–1/4 years, were 1–2 fold the RDAs – dose-response data are not available.

The Australian Polyp Prevention Project on the other hand, a 2-year (and then further 2 years) 2×2×2 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 (see above)^{97,117}. Further analysis of background carotenoid intakes and their effects is underway.

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, 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.

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 (<i>eg in broccoli</i>)	Colon
Resistant starch	Colon

Phytoestrogen

Tamoxifen is an effective management and possibly protective 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 vagina¹²⁷ and bone⁷⁰. It followed 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 at al.⁶⁵. The same may also apply to prostatic cancer in men¹⁴⁰.

Salicylate

Salicylate, possibly even more so than acetylsalicylic acid

(aspirin), through effects on membrane properties may affect cancer expression. Aspirin itself has been shown to be associated with significantly less GI (gastrointestinal) cancer at several sites^{114,125}. Salicylates are present principally on fruits¹¹¹ 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, cryptoxanthin, zeaxanthin) and flavonoids (eg quercetin) may be cancer protective¹¹⁵.

Food pattern

Comment has already been made on the relative merits of snacking in relation to neoplasia and macrovascular disease⁹².

Breakfast as a time of day to achieve a significant fraction of the day's nutrient needs is receiving more attention⁴⁶. 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 health¹²⁶. Certainly, social activity can encourage the consumption of food variety and a correspondingly healthful dietary pattern⁴⁵. 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 food components⁴³.

Table 6. 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	

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

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

There is now evidence that food variety, expressed as a Food Diversity score in the NHANES I⁵⁰ study is powerfully predictive of all-cause mortality, more so far men than women¹⁰. It will therefore be of value in future cancer studies as one way to achieve a mathematical descriptor of the human diet⁴³.

Cancer, immunodeficiency and nutrition

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

- Ageing
- HIV-positivity
- Transplantation with immunosuppression

There are prospects for the nutritional immunomodulation of these situations (Table 6)¹⁷.

Assessing evidence for pathogenetic significance

It is unusual to be able to take one kind of study only as evidence for food or food components as aetiologically or pathogenetically significant in carcinogenesis (Table 7). So by the combination of lines of evidence is more persuasive and may make more meaningful both experimental and observational studies. Even with intervention studies, there situational or food cultural relevance needs to be taken into account.

Table 7. Mechanisms of carcinogenesis.

Stages	I	II	
	Initiation	A	B
		Promotion or inhibition (Reversibility)	Progression (→undifferentiation) Growth control
Mechanisms	Mutational event: Genotoxic chemicals	radiation	
Role of food/nutrition	Yes	Yes	Yes

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'¹²⁰.

Nutritional guidelines for cancer prevention

Such guidelines will undergo progressive refinement and must also be conducive to general health and longevity.

For the present, operational guidelines may be formulated as follows:

- wide variety of biologically distinct foods, especially plant foods and, where possible, low-fat fatty products

- low fat (<20–25% energy intake)
 - modest intake of omega-6, with regular intake of omega-3 polyunsaturated fats and preference for vegetable fat of monounsaturated origin or in intact foods (eg nuts, cereals)
- avoid deep frying
- regular physical activity to increase 'energy through-put'
- avoid salted, cured and pickled food
- modest alcohol intake, preferably with food.

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Nutritional factors in carcinogenesis

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致癌作用的營養因素 摘要

致癌作用的營養因素有不同的評估，這些不同的評估可能有幾方面的理由：（1）由于胚胎和生命早期營養方式和遺傳表達的營養調節而過高地估計了遺傳因素，（2）進食方法的錯誤，（3）營養素致癌學說的局限性，（4）通過免疫監視的間接途徑把營養與癌症聯繫起來。

乳腺癌，結直腸癌，前列腺癌和胰腺癌與營養的關係在迅速變化中，如含雌激素少的食物可能與tamoxifen類似易引起乳腺癌，改變食用富含植物雌激素食物的習慣可能增加男性前列腺癌的危險。盡管已知食物與結直腸癌的關係，如同食物與冠心病的關係一樣，但都市結直腸癌發病率仍持續上升。在工業化社會里，要減少胰腺癌發病可能要從童年，甚至嬰兒期開始改變飲食習慣。

了解現有食物與營養的關係將需要更高水平的具有進食數學模式的營養監測，這將出現新的食品技術，特別是食品設計。