REVIEW ARTICLE

Nutritional factors in carcinogenesis

Mark L. Wahlqvist BMedSc, MD (ADELAIDE), MD (UPPSALA), FRACP, FAIFST, FAFPHM

Department of Medicine, Monash University, Monash Medical Centre, Melbourne, Victoria, Australia.

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 distribution[56]. 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[29,60]. 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 sites[12]. 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 intakes[41]. 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 intake[41]. 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 disease[56].

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

Presented at the 11th Asia Pacific Cancer Conference, Bangkok, Thailand, 16–19 November 1993.
Correspondence address: Professor Mark L. Wahlqvist, Department of Medicine, Monash University, Monash Medical Centre, 246 Clayton Road, Clayton, Victoria 3168, Australia.

- 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 percentage 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 fat[135].

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 tumours[104]. 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[97].

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[92-95] 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 cancer[95] – 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 favourable[49] 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 (*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

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 adenomata[33].

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 (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 dysplasia[67]. 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 and niacin as well. Doses, over 5–1/4 years, were 1–2 fold the RDAs – dose-response data are not available.

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

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 (*eg in broccoli*)	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 vagina[127] and bone[70]. 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 men[140].

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 fruits[111] 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 protective[115].

Food pattern

Comment has already been made on the relative merits of snacking in relation to neoplasia and macrovascular disease[92].

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[126]. Certainly, social activity can encourage the consumption of food variety and a correspondingly healthful dietary pattern[45]. 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 adeuacy if wide enough, and discourages ingestion of excessive quantities of food components[43].

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 I[50] study is powerfully predictive of all-cause mortality, more so far men than women[10]. It will therefore be of value in future cancer studies as one way to achieve a mathematical descriptor of the human diet[43].

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 Initiation	II Post-initiation *A* Promotion or inhibition (Reversibility)	 *B* Progression (→undifferentiation) Growth control
Mechanisms Genotoxic chemicals	Mutational event: specific tumour viruses	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 fairy 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 throughput'
- avoid salted, cured and pickled food
- modest alcohol intake, preferably with food.

References

1 Albanes D. Energy intake and cancer. In Nucozzi MS, Moon TE, eds. Macronutrients: investigating their role in cancer. New York: Marcel Dekker Inc, 1992; 205–229.

2 Albanes, D, Blair A and Taylor PR. Physical activity and risk of cancer in the NHANES I population. Am J Public Health 1989; 79–744.

3 Albanes D and Taylor PR. International differences in body height and weight and their relationship to cancer incidence. Nutr Cancer 1990; 14:69.

4 Armstrong B and Doll R. Environmental factors and cancer incidence and mortality in different countries with special reference in dietary practices. Int J Cancer 1975; 15:617.

5 Ballard-Barbash R, Schatzkin A, Carter CL, Kannel WB, Kreger BE, D'Agostino RB, Splansky GL, Anderson KM and Helsel WE. Body fat distribution and breast cancer in the Framingham Study. JNCI 1990; 82:286–290.

6 Ballard-Barbash R, Schatzkin A, Albanes D, Schiffman MH, Kreger BE, Kannel GL, Anderson KM and Helsel WE. Physical activity and risk of large bowel cancer in the Framingham study. Cancer Res. 1990; 50:3610–3613.

7 Barone J, Taioli E, Herbert JR et al. Vitamin supplement use and risk for oral and esophageal cancer. Nutr Cancer 1992; 18:31–41.

8 Benner SE and Hong WK. Editorial: clinical chemoprevention: developing a cancer prevention strategy. Journal of the National Cancer Institute 1993; 85(18):-1446–1447.

9 Benner SE, Winn RJ, Lippman SM et al. Regression of oral leukoplakia with α-tocopherol: A community clinical oncology program chemoprevention study. J Natl Cancer Inst 1993; 85:44–47.

10 Block G, Patterson B and Subar A. Fruit, Vegetables and Cancer Prevention: a Review of the Epidemiological Evidence. Nutrition and Cancer 1992; 18(1):1–29.

11 Blot WJ, Li J-Y, Taylor PR, Guo W, Dawsey S, Wang G-Q, Yang CS, Zheng S-F, Gail M, Li GY, Yu Y, Liu B-Q, Tangrea J, Sun Y-H, Liu F, Fraumeni JF Jr, Zhang Y-H, Li B. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. Journal of the National Cancer Institute 1993; 85(18):1483–1492.

12 Boffetta P, Barone J, Wynder EL. Leisure time physical activity in a hospital-based population. J Clin Epidemiol 1990; 43(6):569–577.

13 Bounous G, Gold P. The biological activity of undenatured dietary whey proteins: role of glutathione. Clin Invest Med 1990, 1991; 14:296–309.

14 Bounous G, Gervais F, Amer V, Batist G, Gold P. The influence of dietary protein on tissue glutathione and the diseases of ageing. Clin Invest Med 1989; 12:343–9.

15 Butterworth CE Jr, Hatch KD, Macaluso M, Cole P, Sauberlich HE, Soong S-J, Borst M and Baker VV. Folate deficiency and cervical dysplasia. JAMA 1992; 267(4):528–533.

16 Butterworth CE Jr, Hatch KD, Soong SJ, Cole P, Tamura T, Sauberlich HE, Borst M, Macaluso M, Baker V. Oral folic acid supplementation for cervical dysplasia: a clinical intervention trial. Am J Obstet Gynecol 1992; 166(3): 803–9.

17 Chandra RK. Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects. Lancet 1992; 340:1124–1127.

18 Cheng KK, Day NE, Duffy SW, et al. Pickled vegetables in the aedology of oesophageal cancer in Hong Kong Chinese. Lancet 1992; 339:1314–1318.

19 Comstock GW, Bush TL, Helzlsouer K. Serum retinol, beta-carotene, vitamin E, and selenium as related to subsequent cancer of specific sites. Am J Epidemiol 1992; 135:115–121.

20 Conney AH, Wang ZY, Ho C-T, Huang M-T and Yang CS. Inhibitory effect of green and black tea on tumorigenesis in mice. Abstracts XVth International Congress of Nutrition, Adelaid, 26 September–1 October 1993; 381.

21 Cowen LD, O'Connell DL, Criqui MH, Barrett-Connor E, Bush TL, Wallace RB. Cancer mortality and lipid and lipoprotein levels. Am J Epidemiol 1990; 131:468–482.

22 Cramer DW, Willett WC, Bell DA, Ng WG, Harlow BL, Welch WR, Scully RE and Knapp RC. Galactose consumption and metabolism in relation to the risk of ovarian cancer. The Lancet 1989; July 8:66–71.

23 De Waard F and Trichopoulos D. A unifying concept of the aetiology of breast cancer. Int J Cancer 1988; 41:666.

24 Eaton BS, Konner M. Paleolithic nutrition. N Eng J Med 1985; 312:283–289.

25 Foy H, Kondi A. The vulnerable esophagus: riboflavin deficiency and squamous cell dysplasia of the skin and esophagus. JNCI 1984; 941–948.

26 Freudenheim JL, Graham S, Marshall JR, Haughey BP, Cholewinski S, Wilinson G. Folate intake and carcinogenesis of the colon and rectum. Int J Epidemiol 1991; 20(2):368–374.

27 Frisch RE, Wyshak G, Albright NL et al. Lower prevalence of breast cancer and cancers of the reproductive system among former college althletes compared to nonathletes. Br J Cancer 1985; 52:885–891.

28 Gabrial GN, Schrager TF, Newberne PM. Zinc deficiency, alcohol and retinoid: association with esophageal cancer in rats. JNCI 1982; 68:785–789.

29 Gararant DH, Peters JM, Mack TM, Bernstein L. Job activity and colon cancer risk. Am J Epidemiol 1984; 119:1005–1014.

30 Garewal HS, Meyskens FL Jr, Killen D et al. Response of oral leukoplakia to beta-carotene. J Clin Oncol 1990; 8:1715–1720.

31 Gaskill SP, McGuire WL, Osborne CK and Stern MP. Breast cancer mortality and diet in the United States. Cancer Res 1979; 39:3628.

32 Gerhardsson M, Norell SE, Kiviranta H, Pedersen NL, Ahlbom A. Sedentary jobs and colon cancer. Am J Epidemiol 1986; 123:775–780.

33 Giovannucci E, Stampfer MJ, Colditz GA, Rimm EB, Trichopoulos D, Rosner BA, Speizer FE, Willett WC. Folate, methionine, and alcohol intake and risk of colorectal adenoma. J Natl Cancer Inst 1993; 85(11): 875–84.

34 Goodwin JS, Goodwin JM and Garry PJ. Association between nutritional status and cognitive functioning in a healthy elderly population. JAMA 1983; 249(21):2917–2921.

35 Greenberg ER. A clinical trial of beta-carotene to prevent basal-cell and squamous-cell cancers of the skin. The Skin Cancer Prevention Study Group (published erratum appears in N Engl J Med 1991; 325:1324. N Engl J Med 1990; 323:789–795.

36 Gridley G, McLaughlin JK, Block G et al. Vitamin supplement use and reduced risk of oral and pharyngeal cancer. Am J Epidemiol 1992; 135:1083–1092.

37 Guo W, Li JY, Blot WJ et al. Correlations of dietary

intake and blood nutrient levels with esophageal cancer mortality in China. Nutr Cancer 1990; 13:121–127.
38 Harris RE, Wynder EL. Breast cancer and alcohol consumption: a study in weak associations. JAMA 1988; 259:2867–2871.
39 Hebert JR, Miller DR. Methodologic considerations for investigating the diet-cancer risk. Am J Clin Nutr 1988; 47:1068–1077.
40 Henson DE, Block G, Levine M. Ascorbic acid: biologic functions and relation to cancer. J Natl Cancer Inst 1991; 83:547–550.
41 Hirayama T. Relationship of soybean paste soup intake to gastric cancer risk. Nutrition and cancer 1982; 3(4):223–233.
42 Hirayama T. Epidemiology of breast cancer with special reference to the role of diet. Prev Med 1978; 7:173–195.
43 Hodgson JM, Hsu-Hage BH-H and Wahlqvist ML. Food variety as a quantitative descriptor of food intake. Ecology of Food and Nutrition (in press).
44 Hong WK, Lippman S, Itri LM et al. Prevention of second primary tumours with isotretinoin in squamous-cell carcinoma of the head and neck. N Engl J Med 1990; 323:795–801.
45 Horwarth CC. A random population study of the dietary habits of elderly people. PhD thesis. University of Adelaide 1987.
46 Howden JA, Chong YH, Leung SF, Rabuco LB, Sakamoto M, Tchai BS, Tontisirin K, Wahlqvist ML, Winarno FG and Yap M. Breakfast practices in the Asian region. Asia Pacific Journal of Clinical Nutrition 1993; 2(2):77–84.
47 Howe GR, Ghadirian P, Bueno de Mesquita HB, Zatonski WA, Baghurst PA, Miller AB, Simard A, Baillargeon J, de Waard F, Przewozniak K et al. A collaborative case-control study of nutrient intake and pancreatic cancer within the search programme. Int J Cancer 1992; 51(3):365–372.
48 Hunter DJ, Manson JE, Colditz GA, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE and Willett WC. Prospective study of the intake of vitamins C, E, and A and the risk of breast cancer. N Engl J Med 1993; 329:234–40.
49 Jenkins DJA, Wolever TMS, Vuksan V et al. Nibbling versus gorging: metabolic advantages of increased meal frequency. N Engl. J Med 1989; 321:929–934.
50 Kant AK, Schatzkin A, Harris TB, Ziegler RG and Block G. Dietary diversity and subsequent mortality in the First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Am J Clin Nutr 1993; 57:434–40.
51 Kato I, Tomnaga S and Kuroishi T. Relationship between westernization of dietary habits and mortality from breast and ovarian cancer in Japan. Jpn J Cancer res (Gann) 1987; 78:349.
52 Knekt P, Aromaa A, Maatela J et al. Serum selenium and subsequent risk of cancer among Finnish men and women. J Natl Cancer Inst 1990; 82:864 868.
53 Kodama M and Kodama T. Interelation between Western type cancers and non-Western type cancers as regards their risk variations in time and space. II. Nutrition and cancer risk. Anticancer Res 1990; 10:1043.
54 Kolonel LN and Nomura AMY. Dietary intervention trials on prostate cancer. In Micozzi MS and Moon TE, Macronutrients: investigating their role in cancer. New York: Marcel Dekker Inc, 1992: 423–436.
55. Khaw KT, Sneyd M-J Compston J. Bone density parathyroid hormone and 25-hydroxyvitamin D concentrations in middle aged women. BMJ 1992; 305:277.
56 Kromhout D, Bosschieter EB and De Lezenne Coulanders C. The inverse relation between fish consumption and 20-yearly mortality from coronary heart disease, cancer and all causes. The Zutphen Study. Lancet 1982; 2:518–521.
57 Kune GA, Kune S, Watson LF. Body weight and physical activity as predictors of colorectal cancer risk. Nutrition and Cancer 1990; 13:9–18.
58 LaVecchia C, Negri E, Decarli A et al. A case study to cancer in northern Italy. Int J Cancer 1988a; 41:492–498.
60 Lapidus L, Helgesson, Merck C and Bjorntop P. Adipose tissue distribution and female carcinomas. A 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. Int J Obesity 1988; 12:316–368.
61 Lashner BA. Recommendations for colorectal cancer screening in ulcerative colitis: a review of research from a single university-based surveillance program. Am J Gastroenterol 1992; 87(2):168–75.
62 Lauritzen JB, Petersen MM and Lund B. Effect of external hip protectors on hip fractures. Lancet 1993; 341:11–13.
63 Le Marchand L. Anthropometry, body composition, and cancer. In Micozzi ms and Moon E, eds. Macronutrients: investigating their role in cancer. New York: Marcel Dekker Inc, 1992: 321–342.
64 Le Marchand L, Kolonel LN and Yoshizawa CN. Am J Epidemiol 1991; 133:103.
65 Lee HP, Gouley L, Duffy SW, Esteve J, Lee J and Day NE. Dietary effects on breast-cancer risk in Singapore. The Lancet 1991; 337:1197–1200.
66 Levitt AJ, Karlinsky H. Folate, vitamin B12 and cognitive impairment in patients with Alzheimer's disease. Acta Psychiatr Scand 1992; 86:301–305.
67 Li J-Y, Taylor PR, Li B et al. Nutrition intervention trials in Linxian, China: multiple vitamin/mineral supplementational cancer incidence, and disease-specific mortality among adults with esophageal dysplasia. J Natl Cancer Inst 1993; 85:1492–1498.
68 Lipkin M, Friedman E, Winawer SJ, Newmark H. Colonic epithelial cell proliferation in responders and nonresponders to supplemental dietary calcium. Cancer Res 1989; 49:248–254.
69 Love RR. Clinical Trials on Breast Cancer. In: Micozzi ms and Moon TE, eds. Macronutrients: investigating their role in cancer. New York: Marcel Dekker Inc, 1992:377–405.
70 Love RR, Mazess RB, Barden HS, Epstein S, Newcomb PA, Jordan C, Carbone PP and DeMets DL. Effects of tamoxifen on bone mineral density in postmenopausal women with breast cancer. N Eng J Med 1992; 326:852–856.
71 Lyon JL, Mahoney AW, West DW, Gardner JW, Smith KR, Sorenson AW, Stanish W. Energy intake: its relationship to colon cancer risk. JNCI 1987; 78:853–861.
72 MacLennan R, Ward M, Macrae F, Wahlqvist M, Goulston K, Ngu M, Bain C, Russell A. Dietary prevention of large bowled neoplasia. Abstracts of XV International Congress of Nutrition, Adelaide, 26 September–1 October 1993:380.
73 Manousos O, Day NE, Trichopoulos D, Gerovassilis F, Tzonou A. Diet and colorectal cancer: a case-control study in Greece. Int J Cancer 1983; 32:1–5.
74 Matsuzaki T. Longevity, diet and nutrition in Japan: epidemiological studies. Nutrition Reviews 1992; 50(12):355–359.
75 Maynes ST, Graham S, Zheng TZ. Dietary retinol: prevention or promotion of carcinogenesis in humans: (published erratum appears in Cancer Causes Control 1992; 3:184). Cancer Causes Control 1991; 2:443–450.
76 McIntyre A, Gibson PR, Young GP. Butyrate production from dietary fibre and protection against large bowel cancer in a rat model. Gut 1993; 31:386–391.
77 McLaghlin JK, Gridley G, Block G et al. Dietary factors in oral and pharyngeal cancer. JNCI 1988; 15:1237–1243.
78 McMichael AJ. Coffee, soya and pancreatic cancer. Lancet 1981; s:689–690.

79 Micozzi MS. Nutrition, body size, and breast cancer. Yearbook of Physical Anthropology 1985; 28:175–206.
80 Micozzi MS, Breecher GR, Taylor PR, Khachik F. Carotenoid analysis of selected raw and cooked foods associated with a lower risk for cancer. JNCI 1990; 82:282–285.
81 Miller AB, Kelly A, Choi NW et al. Study of diet and breast cancer. Am J Epidemiol 1978; 107:499.
82 Nuñoz N, Wahrendorf J, Bang LJ et al. No effect of riboflavine, retinol, and zinc on prevalence of precancerous lesions of oesophagus. Randomised double-blind intervention study in high-risk population of China. Lancet 1985; 2:111–114.
83 Muñoz N. Hayashi M, Bang LJ et al. Effect of riboflavin, retinol, and zinc on micronuclei of buccal mucosa and of esophagus: a randomized double-blind intervention study in China. JNCI 1987; 79:687–691.
84 National Research Council. Diet and Health, Implications for Reducing Chronic Disease Risk. National Academy Press, Washington, DC, 1989.
85 Negri E, La Vecchia C, D'Avanzo B, Franceschi S. Calcium, dairy products, and colorectal cancer. Nutr Cancer 1990; 13:255–262.
86 Oishi K, Okada K, Yoshida O et al. A case-controlled study of prostatic cancer with reference to dietary habits. Prostate 1988; 12:179–190.
87 Paffenbarger RS, Hyde RT and Wing AL. Physical activity and incidence of cancer in diverse populations: a preliminary report. Am J Clin Nutr 1987; 43:311–317.
88 Paffenbarger RS, Hyde RT, Wing AL and Msieh CC. Physical activity, all-clause mortality and longevity of college alumni. N Engl J Med 1986; 314:605–613.
89 Pariza MW. Dietary fat and cancer risk: evidence and research needs. Ann Rev Nutr 1988; 8:167–183.
90 Pariza MW and Simopoulos AP. Calories and energy expenditure in carcinogenesis. Am J Clin Nutr 1986; 45(suppl):149–272.
91 Phillips RL, Snowdon DA. Association of meat and coffee use with cancers of the large bowel, breast and prostate among Seventh-day Adventists: Preliminary results. Cancer Res 1983; 45(Suppl): 2403–2408.
92 Potter JD. Epidemiology of diet and cancer: evidence of human maladaption. In: Macronutrients: investigating their role in cancer. Micozzi MS and Moon TE, eds. New York: Marcel Dekker Inc; 1992:55–84.
93 Potter JD. The epidemiology and prevention of pancreas cancer. In: Zatonski W, et al., eds. Cancer Prevention Vital Statistics to Intervention. Warsaw, PA: Interpress; 1990.
94 Potter D, Graves KL. Diet and Cancer: evidence and mechanisms – an adaptation argument. In: Rowland I et al., eds. Nutrition Toxicity and Cancer. USA: CRC Press; 1991.
95 Potter D, McMichael AJ. Diet and cancer of the colon and rectum. A case-control study. JNCI 1986; 76:557–569.
96 Reddy BS. Animal experimental evidence on macronutrients and cancer. In: Micozzi MS and Moon TE, eds. Macronutrients: investigating their role in cancer. New York: Marcel Dekker Inc; 1992.
97 Regester GO. Whey protein based functional foods. National Food Authority Workshop, 5–6 October 1993, Canberra.
98 Rohan TE, McMichael AJ and Baghurst PA. A population-based case-control study of diet and breast cancer in Australia. Am J Epidemiol 1988; 128:478.
99. Rose DP. Dietary factors and breast cancer. Cancer Surv 1986; 5:671–687.
100 Rose DP, Boyar AP, Wynder EL. International comparisons of mortality rates for cancer of the breast, ovary, prostate, and colon, and per capita food consumption. Cancer 1986; 58:2363–2371.
101 Schatazkin A, Carter CL, Green SB et al. Is alcohol consumption related to breast cancer? Results from the Framingham Heart Study. JNCI 1989; 81:31–35.
102 Schatzin A, Jones Y, Hoover RN et al. Alcohol consumption and breast cancer in the epidemiologic follow-up study of the first National Health and Nutrition Examination Survey. N Engl J Med 1987; 316:1169–1137.
103 Schatzkin A, Lanza E and Ballard-Barbash R. The case for a dietary intervention study of large bowel polyps. Cancer Prev 1990; 1:106.
104 Shaw P, Tardy S, Benito E, Obrador A, Costa J. Occurrence of K1-Ras and P53 mutations in primary colorectal tumors. Oncogene 1991; 6(11):2121–2128.
105 Shu XO, Gao YT, Yuan JM, Ziegler RG and Brinton LA. Dietary factors and epithelial ovarian cancer. Br J Cancer 1988; 59:92.
106 Slattery ML, Schumacher MC, Smith KR, West DW and Abd-Elghany N. Physical activity, diet and risk of colon cancer in Utah. Am J Epidemiol 1988a; 128:989–999.
107 Slattery ML, Sorenson AW and Ford MH. Dietary calcium intake as a mitigating factor in colon cancer. Am J Epidemiol 1988b; 128:504–514.
108 Stacewicz-Sapuntzakis M, Bowen PE, Kikendall JW and Buress M. Simultaneous determination of serum retinol and various carotenoids: their distribution in middle-aged men and women. J Micro Analysis 1987; 3:27–45.
109 Stich HF, Rosin MP and Hornby AP. Remission of oral leukoplakias and micronuclei in tobacco/betel quid chewers treated with beta-carotene and with beta-carotene plus vitamin A. Int J Cancer 1988; 42:195–199.
110 Stich HF, Rosin MP and Vallejera MO. Reduction with vitamin A and beta-carotene administration of proportion of micronucleated buccal mucosal cells in Asian betal nut and tobacco chewers. Lancet 1984; 1:1204–1206.
111 Swain A, Dutton S and Truswell AS. Salicylates in Australian foods. Proc Nutr Soc Aust 1982; 7:163.
112 Tajima K, Hirose K, Nakagawa N, Juroshishi T and Tominaga S. Urban-rural difference in the trend of colorectal cancer mortality with special reference to the subsites of colon cancer in Japan. Gann 1985; 76:717–728.
113 Taylor HL and Keys A. Adaptation to caloric restriction. Science 1950; 112:215.
114. Thum MJ, Namboodiri MM, Calle EE, Flanders WD and Heath CW. Aspirin use and risk of fatal cancer. Cancer Research 1993; 53:1322–1327.
115 Thurnham DI, Zheng S-F, Munoz N et al. Comparison of riboflavin, vitamin A, and zinc status of Chinese populations at high and low risk for esophageal cancer. Nutr Cancer 1985; 7:131–143.
116 Trock B, Lanza E and Greenwald P. Dietary fibre, vegetables and colon cancer: critical review and meta-analysis of the epidemiologic evidence. JNCI 1990; 82:650–661.
117 van Poppel G, Kok FJ, Hermus RJ. Beta-carotene supplementation in smokers reduces the frequency of micronuclei in sputum. Br J Cancer 1992; 66:1164–1168.
118. Vargas PA and Alberts DS. Clinical trials on colorectal cancer. In: Micozzi MS and Moon TE, eds. Macronutrients: investigating their role in cancer. New York:P Marcel Dekker Inc; 1992:407–421.
119 Vena E, Graham S, Zielezny M et al. Lifetime occupational exercise and colon cancer. Am J Epidemiol 1985; 122:357–365.
120 Wahlqvist ML. Non-nutrients in foods, implications for the food industry. Food Australia 44(12):558-560, 1992.
121 Wahlqvist ML, Huang SS and Worsley A. Use and abuse of vitamins, Second edition. Melbourne, Sun Books, The MacMillan Company of Australia, 1983.
122 Wahlqvist ML. Vitamin A and cancer. Proceedings of the 5th Asian Congress of Nutrition, Osaka, Japan, October 26–29, 1987:400–403.
123 Watanabe S, Arimoto H. Long term trends in cancer mortality rates from 1955 to 1987 in Japan. Jpn J Clin Oncol 1989; 19:305–317.

124 Weisburger JH. Mechanisms of macronutrient carcinogenesis. In: Miccozzi MS and Moon, TE, eds. Macronutrients: investigating their role in cancer. New York; Marcel Dekker Inc; 1992:3–31.
125 Weissmann G. Aspirin. Scientific American, January 1991:58–64.
126 Welin L, Tibblin G, Svardsudd K, Tibblin B, Ander-Peciva S, Larsson B and Wilhelmsen L. Prospective study of social influences on mortality. Lancet 1985; 1:915–918.
127 Wilcox G, Wahlqvist ML, Burger HG and Medley G. Oestrogenic effects of plant-derived foods in postmenopausal women. BMJ 1990; 301:905–906.
128 Willemsen W, Kruitwagen R, Bastianns B, Hanselaar T and Rolland R. Ovarian stimulation and granulosa-cell tumour. Lancet 1993; 341:986–988.
129 Willett W. The search for the causes of breast and colon cancer. Nature 1989; 338:389–394.
130 Willett WC, Browne ML, Bain C et al. Relative weight and risk of breast cancer among premenopausal women. Am J Epidemiol 1985; 122:731–740.
131 Willett WC, Stampfer MJ and Colditz GA et al. Dietary fat and the risk of breast cancer. N Engl J Med 1987; 316:22–28.
132 Willett WC, Stampfer MJ, Colditz GA et al. Moderate alcohol consumption and the risk of breast cancer. N Engl J Med 1987b; 316:1174–1180.
133 Willett WC, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986; 124:17–27.
134. Willett WC, Stampfer MJ, Colditz GA, Rosner BA and Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med 1990; 323:1664–1672.
135 Xu D-D. A nutrition-epidemiological approach on breast and colon cancer in Shanghai. Proceedings of the 5th Asian Congress of Nutrition, Osaka, Japan, October 26–29, 1987:378–380.
136 Young TB. A case-control study of breast cancer and alcohol consumption habits. Cancer 1989; 64:552–558.
137 Young TB and Wolf DA. Case-control study of proximal and distal colon cancer and diet in Wisconsin. Int J Cancer 1988; 42:167–175.
138 Yu SY, Chu Y, Gang XL et al. Regional variation of cancer mortality and its relation to selenium levels in China. Biol Trace Elem Res 1985; 7:21–29.
139 Zaridze D, Evstifeeva T. and Boyle P. Chemoprevention of oral leukoplakia and chronic esophagitis in an area of high incidence of oral and esophageal cancer. Ann Epidemiol 1993; 3:225–234.
140 Adlercreutz H, Markkanen H, Watanabe S. Plasma concentrations of phyto-estrogens in Japanese men. Lancet 1993; 342:1209–1210.

Nutritional factors in carcinogenesis

Mark L. Wahlqvist

Asia Pacific Journal of Clinical Nutrition, 2:141–148

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喂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系起來。

乳腺癌，結直腸癌，前列腺癌和胰腺癌與營養的關系在迅速變化中，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系，如同食物與冠心病的關系一樣，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系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。