Vitamins A, C, E and β-carotene as protective factors for some cancers

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The importance of the antioxidant micronutrients vitamins A, C, E and β-carotene in cancer prevention is currently a widely debated human health issue. Generally supported by laboratory findings, and persuasively linked to the lower cancer risk associated with high intakes of fruit and vegetables, the hypothesis is now being tested in many prospective studies around the world. Increasingly, oxidative damage has been implicated in the etiology of several degenerative diseases including cancer, thus highlighting the need to ensure replete antioxidant nutriture as a central measure in preventive medicine.

Introduction

Environmental factors are considered to be responsible for the development of 80–90% of cancers in humans, of which 30–60% exhibit strong dietary links. Overall it has been estimated that appropriate dietary alterations could prevent about ⅓ of cancer cases in humans[1]. Such strategies would include on the one hand the avoidance of carcinogenic substances in food, while on the other attempting to increase the intake of dietary anticarcinogens.

Dietary anticarcinogens

Many substances in food have been nominated as candidate anti-carcinogens, ranging from macronutrients such as fibre and calcium to a large number of minor dietary constituents including several micronutrients. The mechanisms whereby these substances may act protectively are widely diverse and are summarized in Table 1.

Pro-oxidants, antioxidants and carcinogenesis

Of particular current interest are the antioxidant micronutrients which include vitamins A, C, E and the carotenoids and which are considered to act protectively in several ways including limiting oxidative free radical damage to DNA and other cellular macromolecules (Figure 1), (Table 2).

Table 1. Mechanisms of cancer protection by minor dietary constituents*.

1.	Prevent carcinogen formation
2.	Block carcinogen action
	a) reduce metabolic activation
	b) increase detoxification (cytochrome P-450, conjugation)
3.	Reduce free radical related cellular damage
	a) antioxidants
4.	Enhance error-free DNA repair
5.	Suppress cancer expression (reversible)
	a) oncogene control
	b) cellular differentiation
6.	Enhance immunosurveillance

* Developed from references[2-5].

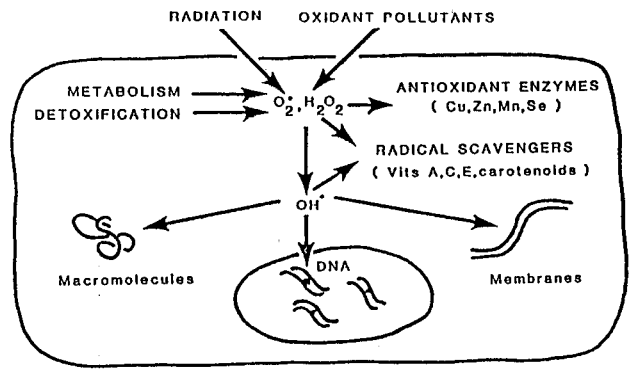

Figure 1. Cellular free radical-related damage and antioxidant micronutrient defence.

Table 2. Possible mechanisms of vitamins A, C, E and β-carotene vitamins in cancer protection*.

Mechanism		Active Agent
1.	Reduced carcinogen formation	Vitamins C, E
2.	Reduced oxidative damage	Vitamins A, C, E, β-carotene
3.	Reduced oncogene expression (myc, ras)	Vitamins A, E
4.	Reduced cell signalling systems (AC, PKC)	Vitamins A, E, β-carotene
5.	Induced differentiation of transformed cells	Vitamins A, C, E, β-carotene
6.	Enhanced immunocompetence	Vitamins A, C, E, β-carotene

*Developed from references[1-4,6-8].

Certainly, many pro-oxidants are potent experimental carcinogens (Table 3), while many antioxidants have been demonstrated to be significantly protective against cancer.

Evidence for the role of antioxidants as antimutagens/anticarcinogens has emerged from three areas of study.

Table 3. Pro-oxidants as carcinogens[7].

Radiation (X and UV)	Xenobiotic metabolism
Hyperbaric oxygen	daunorubicin
Peroxides	streptonigrin
Peroxisome proliferators	adriamycin
clofibrate	mitomycin C
nafenopin	polycyclic aromatic hydrocarbons
Modulators of electron transport chain	Antioxidant inhibitors
rotenone	phorbol myristate acetate
phenobarbital	Asbestos

1 In vitro experiments with cells in culture exposed to pro-oxidant mutagens/carcinogens and various anti-oxidants.
2 In vivo studies with experimental animals following a similar experimental protocol.
3 Human epidemiological surveys.

Both the experimental animal studies and the human surveys are especially relevant to the assessment of the antioxidant vitamins as important dietary anticarcinogens.

Table 4. Vitamins A, C, E and β-carotene as anticarcinogens – animal studies*.

Nutrient	Species	Organ	Carcinogen**	Overall effect on carcinogenesis
Vitamin A	rat	colon	NG	↑ if deficient
(Retinoids)	rat	lung	MCA	↑ if deficient
	hamster	lung	BP/MCA	↓→↑
	mouse	skin	BP/DMBA-TPA	↓
	rat	mammary gland	DMBA/NU/virus	↓
	mouse	mammary gland	virus	↓
	rat	bladder	NU/NA	↓→
	mouse	bladder	NH	↓
Vitamin C	mouse	skin	UV/DMBA-CO	↓
	hamster	naso-trachea	Cig-Smoke/NA	↓/↑
	mouse	lung	NA	↓
	mouse	lung	fibreglass	↓
	hamster	kidney	estrogen	↓
	rat	colon	DMH	↓→↑
	mouse	colon	DMH	→
	rat	mammary gland	DMBA	→
	rat	bladder	NA	→↑
	mouse	bladder	NA	↓
	rat	sarcoma	BP	↓
Vitamin E	mouse	skin	DMBA-CO/UV	↓/↓
	hamster	mouth	DMBA	↓
	rat	mammary gland	DMBA/DN/NU	↓→
	mouse	forestomach	DMBA	→
	rat	colon	DMH/DMBA	↓→/↑
	mouse	colon	DMH	↓↑
	rat	liver	DMAB/NA	↓
	hamster	liver	NA	↓
β-Carotene	mouse	skin	UV	↓
	rat	salivary gland	DMBA	↓
	hamster	mouth	DMBA	↓
	mouse	mammary gland	MOP	↓
	rat	stomach	NG	↓→
	mouse	colon	DMH	↓
	mouse	sarcoma	virus	↓

*Compiled from references [2,6,9-11].

BP – benzo (a) pyrene
CO – croton oil
DMAB – dimethylazobenzene
DMH – dimethylhydrazine
DN – daunomycin
MCA – methylcholanthrene
MOP – methoxypsoralen
NA – nirosamine
NG – nitrosoguanidine
NU – nitrosourea
TPA – phorbol acetate

↑ increase
→ no effect
↓ decrease

Vitamins A, C, E and carotene: animal studies

Several hundred experimental studies have addressed the issue of the antioxidant vitamins and β-carotene as anticarcinogens with respect to a variety of potent carcinogens in several animal species – often with equivocal results (Table 4).

Overall however, the weight of evidence points persuasively to protection by each of the agents with respect to skin carcinogenesis, retinoids in relation to the mammary gland, vitamin C with respect to the lung, vitamin E for tumours of the mouth and liver, while β-carotene appears to be generally protective for the mouth, mammary gland and colon.

Vitamins A, C, E and carotene: human studies

To date, most human studies concerning the anticancer activity of vitamins A, C, E and the carotenoids have been of a non-experimental epidemiological nature, which, while providing valuable leads to the underlying science, cannot because of methodological limitations, draw precise conclusions with respect to single nutrients (Table 5).

Table 5. Categories of human diet-cancer studies*.

Epidemiological studies (non-experimental)

Dietary-intake

1. Food disappearance data – good for international trends but many confounders/associations.
2. Cohort studies (prospective) – excludes cancer as a confounder but associations still present.
3. Case control studies (retrospective) – fewer confounders but dietary history data imprecise.

Nutrient Status

1. Tissue analysis – suitable for case or cohort studies but potential bias due to presence of cancer at the time of sampling.

Intervention studies (experimental)

Preclinical Trials (3 stages)

1. Selection of agent.
2. Test effectiveness of agent.
3. Establish pharmacology and toxicology.

Clinical Trials (3 phases)

1. Establish dose and safety in humans (chemoprevention vs treatment).
2. Establish effectiveness of agent in humans.
3. Conduct human trials for risk reduction (prospective, at risk populations).

*Compiled from references[4-6,12,13].

Nevertheless, the very large number of studies performed so far point overwhelmingly to protection against many forms of cancer by high intakes of fruit and vegetables (Table 6), with strong associations emerging in some cases between the estimated dietary intake or monitored nutrient status of the particular micronutrients.

In addition, some use has been made clinically, and in an experimental setting, of vitamins A, C, E and carotenoids in cancer therapy (Table 7), but detailed discussion of this topic is outside the scope of this review.

Clearly, very much more definitive data will become available over the next decade from the many human intervention trials which are now under way around the

Table 6. A, C and E vitamins and β-carotene as anticarcinogens – human studies*.

Agent	Target organ	Overall cancer risk
Fruit & Vegetables	all sites	↓
	mouth, larynx, esophagus	↓
	stomach, colorectum	↓
	pancreas, lung, bladder	↓
	cervix, endometrium	↓
Vitamin A (Retinoids)	skin	↓
	mouth (leukoplakia)	↓
	esophagus, bladder	↓
	lung	↓→
Vitamin C	mouth	↓→
	larynx, esophagus, stomach	↓
	colorectum	↓→
	pancreas, cervix	↓
	lung	↓→
Vitamin E	all sites	↓→
	esophagus, stomach	↓→
	intestine	→
	breast	↓→ (↓ selenium aggravates)
	pancreas, bladder	↓→
β-Carotene	skin (melanoma)	→
	mouth	↓→
	lung, esophagus, stomach	↓
	pancreas, bladder, colorectum	↓→
	breast, cervix, prostate	↓→

*Compiled from references[1,5,6,9,11,13-20] and include epidemiological studies of all types, and assessment of nutrient status by inference from dietary data and by analysis of levels in blood serum of A, C and E vitamins and β-carotene.

world. Table 8 summarizes some of the major intervention programs being conducted by the USA National Cancer Institute, and some by Australian workers. The magnitude of resources committed to these studies bears witness to the strong belief among nutritional scientists that dietary antioxidants may indeed offer a valuable tool in cancer prophylaxis.

Table 7. Use of A, C and E vitamins and β-carotene in cancer therapy*.

Agent	Condition
Vitamin A (Retinoids)	actinic keratosis, keratoacanthoma
	oral leukoplakia
	lung metaplasia
	post surgery ± chemo/radiotherapy
Vitamin C	–
Vitamin E	–
β-Carotene	oral leukoplakia
	post surgery ± chemo/radiotherapy

*Compiled from references[5,14,21,22].

Interpreting the present dilemma

In the mean time, before data from the definitive intervention trials is forthcoming what broad conclusions may be drawn from existing findings? Clearly, the evidence for protection by high intakes of fruit and vegetables is impressive and argues strongly for continuing nutritional education along these lines, since these foodstuffs contain many other putative protective factors as minor dietary constituents apart from the antioxidants.

However, in terms of current recommended dietary intakes (RDIs) it should be noted that the very high levels of consumption of fruit and vegetables needed to confer protection against cancer, when extrapolated to

Table 8. Some current chemoprevention trials with A, C or E vitamins or β-carotene in humans*.

Agent	Target organs	Risk group	No. of studies	Location
Vitamin A (Retinoids)	all sites	dental nurses	1	USA
	skin	keratoses, BCC**	3	USA
	lung	asbestos(is), smokers	4	Australia, USA
	cervix	dysplasia	1	USA
	colon	polyposis	1	USA
	colon/ rectum	polyposis	1	USA
Vitamin C	skin	BCC	1	USA
	colon	adenomas, polyposis, normal	3	USA
Vitamin E	all sites	dental nurses	1	USA
	skin	BCC	1	USA
	lung	smokers	2	USA
	colon	polyposis, normal	3	USA
	colon/ rectum	polyposis	1	USA
β-Carotene	all sites	physicians	1	USA
	skin	BCC, albinos	3	Australia, Tanzania, USA
	lung	asbestos(is) smokers, aged	5	Australia, Finland, USA
	esophagus	dysplasia	2	China, USA
	colon	adenomas, polyposis	3	Australia, USA
	cervix	dysplasia	2	Australia, USA
Multivitamins	all sites	–	1	USA
	esophagus	high risk areas, general	1	China, USA

*Compiled from references[12,23].
**Basal cell carcinoma.

the putative micronutrients involved, reflects intakes considerably in excess of current RDI's. Unquestionably, fruits and vegetables are complex mixtures of many food factors and there can be no firm assurance that the nominated antioxidant micronutrients are the main active agents – except for the strong support from experimental studies with animals, and several recent human surveys linking reduced risk of cancer specifically to antioxidant supplementation (Table 9). There seems little doubt that the stage has now been reached when nutritional scientists need to consider carefully the criteria on which the requirements for some micronutrients are based. Prevention of overt deficiency disease or apparently adequate reserves may not establish the requirement for optimum health and protection against degenerative disease. For example, in rats it appears that normal growth can be obtained on a diet containing 7.5mg vitamin E/kg. Myopathy can be prevented with 15mg/kg and red cell haemolysis avoided with 50mg of vitamin E/kg.

Table 9. Evidence of cancer protection by A, C and E vitamin supplementation*.

Agent	Target organ	Risk: odds ratio	Dose
Vitamin E	mouth and pharynx	0.5	usage of supplements
Vitamin C	colon and rectum	0.5	>230mg/day
Vitamin C	lung cancer (smokers)	0.3	high in diet plus supplements

*Compiled from references[19,24,25].

However, the mitogenic response of T and B lymphocytes, which reflects a measure of immunocompetence, increases linearly with a rise in serum vitamin E levels between 0.4–18μg/ml obtained from diets containing 200mg/kg[26].

The possibility therefore arises that the evolution of certain aspects of human micronutrient metabolism did not take place in the context of present dietary intakes and lifestyle factors. Paleolithic man for example is estimated to have consumed around 400mg of vitamin C each day[27]. The diet scientists perceive today to be well balanced may conceivably not be precisely the optimum for maximum human health.

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維生素A、C、E和β－胡蘿卜素作爲某些癌症的保護因子

摘　要

抗氧化劑微觀營養素，維生素A、C、E和β－胡蘿卜素在癌症預防的價值，是最近廣泛討論的人體健康問題。一般得到實驗室結果的支持，并有説服力地把低癌危險與多食蔬菜、水果聯系起來。目前世界上許多預期的研究正對此假説進行驗證。愈來愈多地，氧化損害已牽涉到幾種退行性疾病，包括癌症的病因，因而作爲預防醫學的中心措施，應集中注意力保證充分供應抗氧化劑營養素。