

Meeting Report

An International Evaluation of the Cancer Preventive Potential of Carotenoids

Harri Vainio¹ and Matti Rautalahti

Unit of Chemoprevention, International Agency for Research on Cancer, 69372 Lyon, France

Abstract

The IARC convened a Working Group of experts in December 1997 to evaluate the cancer-preventive potential of carotenoids and to compile the second volume of the *IARC Handbooks of Cancer Prevention*.

In observational epidemiological studies, β -carotene is associated with reduced risks for cancer at many but not all sites. It is unclear, however, to what extent β -carotene itself is responsible for the decreased risks observed. Three large, randomized, placebo-controlled clinical trials indicate, however, that, in substantial doses, supplementation with β -carotene not only does not prevent lung cancer but may actually increase the risk among individuals initially at high risk of lung cancer. These trials do not provide clear evidence concerning cancers at other specific sites. Thus, the Working Group considered that there is evidence suggesting a lack of cancer-preventive activity for β -carotene when it is used as a supplement at high doses. At usual dietary levels of β -carotene, the evidence for cancer-preventive activity was considered inadequate. However, there is sufficient evidence that β -carotene has cancer-preventive activity in experimental animals, based on models of skin carcinogenesis in mice and buccal pouch carcinogenesis in hamsters.

The observational epidemiological data on α -carotene, lycopene, and lutein are much less extensive than those for β -carotene. For canthaxanthin, there are no published data regarding associations with cancer risk. These carotenoids have not been studied in human trials for cancer prevention. In animal models, there is sufficient evidence for canthaxanthin and limited evidence for α -carotene, lycopene, and lutein of cancer-preventive activity.

Pending further research, supplemental β -carotene, canthaxanthin, α -carotene, lutein, and lycopene should not be recommended for cancer prevention in the general population.

Introduction

Many epidemiological studies conducted during the late 1970s and early 1980s found negative associations between estimated

intakes of vitamin A (retinol) or β -carotene (provitamin A) and the risk for developing cancer at various sites. Following these observations, a number of authors postulated that β -carotene itself, without transformation into retinol, might protect against cancer by formation of antioxidants. This suggestion captured the imagination of many workers and stimulated much research (1). The second volume of the *IARC Handbooks of Cancer Prevention* (2) critically evaluates work, particularly that carried out in the last two decades, that is relevant to the potential of carotenoids in cancer prevention. An enormous volume of experimental research on the anticancer effects of β -carotene and other dietary and nondietary carotenoids resulted from the enthusiasm following the observations of an inverse association between dietary β -carotene and cancer risk. The *Handbook* also describes and evaluates the outcome of the large intervention trials that were kindled by enthusiasm for the hypothesis and made possible by the availability of β -carotene supplements. Attempts were made to define the direction that research is currently taking and the areas in which more research is still needed.

Carotenoids

Carotenoids occur in all of the three domains of life, *i.e.*, in the Eubacteria, the Archea, and in the Eucarya. More than 600 naturally occurring carotenoids are known today (3), and some 100 or so of these are likely to be present in the human diet. Given the large number of carotenoids in nature, detailed systematic nomenclature has been developed for these compounds (4). The *Handbook* deals specifically with those that are found most prominently in human blood and tissues and with which the most extensive studies of cancer prevention have been undertaken. The term "carotenoid" covers all of these compounds. The term "carotene" is restricted to the hydrocarbons, that is, compounds containing only hydrogen and carbon. Carotenoids containing oxygen functions are known as "xanthophylls." Provitamin A carotenoids include β -carotene and other compounds that contain one unsubstituted β ring.

Recently, it was demonstrated by the analysis of serum and human breast milk that ~20 dietary carotenoids from fruits and vegetables may be absorbed and metabolized by humans (5); however, only six or seven have been studied in any depth, of which three are provitamin A carotenoids (β -carotene, α -carotene, and β -cryptoxanthin), and the others (lycopene, lutein, and zeaxanthin) lack this quality. The carotenoids are hydrophobic, lipophilic substances that, after ingestion, are absorbed in the small intestine with other lipids absorbed and appear in lipoproteins of the plasma (6). The types and amounts of carotenoids in the plasma reflect those in the diet (7). The state in which the carotenoids occur in the food matrix, *e.g.*, crystalline or not, their concentration, the availability of fat or oil, and the presence of bile acids are major factors in determining bioavailability (8). In the body, all carotenoids are found in lipid environments, especially fatty tissues and membranes (7).

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¹ To whom requests for reprints should be addressed.

Their presence in membranes may be important in relation to their biological actions.

The major known function of carotenoids in humans is as precursors of vitamin A. Only 50 of the carotenoids in nature, however, serve this role (9). The major pathway of enzymatic conversion is central cleavage of the carotenoid molecules, although asymmetric cleavage can also occur (10, 11). The long system of conjugated double bonds that constitutes the light-absorbing chromophore of the carotenoids also makes these molecules rather unstable and very reactive toward oxidizing agents and free radicals (12). They can have antioxidant or pro-oxidant actions *in vitro* (13). Although antioxidant activity *in vivo* has not been proven, this has been proposed as a possible mechanism by which carotenoids could protect against cancer and other degenerative diseases.

Oxidative processes may damage macromolecules such as proteins, lipids, and DNA bases. Such damage may affect proper functioning of cells and contribute to the development of cancer, cardiovascular, and other degenerative disease. However, it should be kept in mind that oxidative processes are also a necessary part of essential biological functions in cells, including those involved in intracellular signal transduction and control of cell proliferation or apoptosis (14). Thus, the health of an organism depends on the balance between oxidants and antioxidants.

Issues in Research Regarding Carotenoids and Human Cancer

Extensive research regarding the effect of carotenoids on carcinogenesis has used *in vitro* systems, animal studies, human epidemiological studies, and human clinical trials. The application of all these different disciplines will be needed to understand the possible effects of carotenoids in the prevention of cancer. However, the different research domains have suggested different mechanisms or even different effects (15–17). Such discrepancies emphasize that each of the research modalities has limitations and may not provide relevant information for cancer prevention as it is actually conducted. *In vitro* and animal studies rely on biological models of carcinogenesis, which may not actually correspond to human cancer. Animal models of cancer often involve particular carcinogens and a dosing schedule that is much more rapid than most human carcinogenic exposures. In addition, absorption and transport of carotenoids may differ between humans and animals, further complicating extrapolation from animal studies to human cancer.

Epidemiology is also subject to several potential limitations. Estimates of dietary intake of carotenoids using questionnaires in combination with food composition tables or biomarkers of nutritional exposure may have only limited validity. This is, because questionnaires tend to reflect recent intake rather than intake at the time of cancer induction. Furthermore, until recently, dietary databases did not contain data on the content of specific carotenoids in food items (18, 19). Confounding is a second major issue in nutritional epidemiology. Specific chemical food constituents tend to cluster by food group (*e.g.*, vegetables and fruits are main sources not only of carotenoids but also of other substances that have also been postulated to protect against cancer). Because these other nutrients may also have cancer-protective properties, they may underlie an apparent inverse association between carotenoid intake and cancer risk. Associations with intermediate end points, increasingly used in nutritional epidemiology, may not parallel those for cancer itself (20). Indeed, it has been difficult

even to define what is required for an end point to be a valid intermediate marker of cancer.

Randomized intervention trials can be used to avoid the problems of exposure measurement and confounding that beset observational studies. However, the evidence from clinical trials is restricted to the doses given, the duration, and the stage of natural history of the cancer under study (21). For possible chemopreventive agents such as the carotenoids, the agents used or the way they are administered in clinical trials may also differ in important ways from the situation that holds when carotenoids are obtained from foods. Thus, observational studies on nutrient-disease relations and intervention studies using an isolated nutrient do not necessarily examine the same questions.

Cancer-preventive Effects

The results of epidemiological studies, viewed in aggregate, do not support the notion that β -carotene has generalized cancer-preventive effects. The observational data suggesting cancer-preventive effects are most consistent for lung, oral, and pharyngeal cancers, the incidences of which tend to be inversely related to β -carotene (or provitamin A carotenoid) intake or blood concentrations (Table 1). One difficulty in interpreting these findings is that β -carotene may be only a marker of the intake of other beneficial substances in fruits and vegetables or perhaps other lifestyle habits.

No clinical trial of β -carotene as a single agent, however, has shown a reduction in the risk for cancer at any specific site, and there is evidence of an increase in the risk for lung cancer among smokers and asbestos workers receiving β -carotene supplements at high doses, which resulted in blood concentrations an average of 10–15 times higher than normal (Refs. 22 and 23; Table 2). It is worth noting that the information from clinical trials reflects, at most, the first 12 years of intervention (24), and, at present, there are no data on the possible effects of longer intervention. There is virtually no information on β -carotene supplementation early in the carcinogenic process. Last, the doses used in the intervention trials greatly exceeded those consumed in normal diets. There is only limited and inconsistent human data with regard to carotenoids other than β -carotene.

The results of most of the experimental studies in animals were consistent with protective effects of β -carotene and canthaxanthin and, to lesser extent, α -carotene, lutein, and lycopene in certain sites.

Evaluation

There is evidence suggesting a lack of cancer-preventive activity in humans for β -carotene when it is used as a supplement at high doses. There is inadequate evidence with regard to the cancer-preventive activity of β -carotene at the usual dietary levels. There is inadequate evidence with respect to the possible cancer-preventive activity of other individual carotenoids.

In experimental animals, there is sufficient evidence for cancer-preventive activity of β -carotene and canthaxanthin. For β -carotene, this evaluation is based on models of skin carcinogenesis in mice and buccal pouch carcinogenesis in hamsters. Findings in models of liver carcinogenesis in rats, colon carcinogenesis in rats, and pancreatic carcinogenesis in rats and hamsters provide further support for this conclusion. For canthaxanthin, the evaluation is also based on models of skin carcinogenesis in mice and buccal pouch carcinogenesis in hamsters. Findings in models of rat tongue and mouse stomach

Table 1 Epidemiological studies on carotenoids and cancer reviewed in the Handbook

	Serum studies				Dietary studies			
	Retrospective ^a		Prospective ^a		Retrospective ^a		Prospective ^a	
	<i>n</i>	Inverse association ^b	<i>n</i>	Inverse association ^b	<i>n</i>	Inverse association ^b	<i>n</i>	Inverse association ^b
Lung	5	5	10	6	22	8	9	1
Stomach	1	1	5	2	10	5	1	0
Colorectal	1	0	8	0	15	4	3	0
Bladder	1	0	5	0	7	1	1	0
Breast	7	3	4	0	21	9	7	0
Prostate	2	1	4	0	8	2	3	2
Cervix	8	6	2	1	6	2	0	0
Pancreas	0	0	3	1	7	2	1	0
Upper aerodigestive ^c	4	2	3	3	19	6	1	0
Skin	3	1	5	1	2	0	0	0
Liver	2	2	1	0	2	0	0	0
Endometrium	1	0	1	0	4	2	0	0
Ovary	1	0	2	0	6	2	0	0
Kidney	1	1	2	0	2	0	0	0
Leukemia, lymphoma	1	1	2	1	1	0	0	0
Brain, central nervous system	2	1	2	0	0	0	0	0

^a Retrospective refers to case-control studies, and prospective refers to cohort and nested case-cohort studies.

^b Inverse association refers to a statistically significant ($P < 0.05$) reduction in cancer risk between the highest and lowest category of intake or serum level or reduced mean serum carotene level among cases.

^c Oral, pharynx, larynx, and esophagus.

Table 2 Primary cancer prevention trials using β -carotene and the effect of β -carotene supplementation on cancer incidence

Variable	Linxian (25)	ATBC (22)	CARET (23)		PHS (24)
			Asbestos-exposed	"Heavy smokers"	
No. of subjects	29,584	29,133	4,060	14,254	22,071
Age (yr)	40–69	50–69	50–69	50–69	40–84
Smoking prevalence (%)	30	100	39	66	11
Study design	Fractional factorial: four types of supplement combinations and placebo in eight groups ^a	2 × 2 factorial: β -carotene and α -tocopherol	β -Carotene combined with retinol		2 × 2 factorial: β -carotene and aspirin
Dose of β -carotene	15 mg/day	20 mg/day	30 mg/day		50 mg/2 days
Duration (yr)	5	5–8 (median, 6.1)	4 (mean)		11–14 (mean, 12)
Predefined end points	Esophageal and stomach cancer incidence and mortality	Incidence of lung cancer and other major cancers	Incidence of lung and other cancers		Cardiovascular diseases and lung cancer incidence
Stomach cancer incidence	0.84 (0.71–1.00)	1.25 ^b (NS)			
Esophageal cancer incidence	1.02 (0.87–1.19)				
Lung cancer incidence	[mortality = 0.55 (0.26–1.14)]	1.16 (1.02–1.33)	1.28 (1.04–1.57)		
Nonsmokers					0.78 (0.34–1.79)
Current smokers		1.16 (1.02–1.33)	1.40 (1.10–1.80)		0.90 (0.58–1.40)

^a Supplement combinations were as follows: A, retinol and zinc; B, riboflavin and niacin; C, vitamin C and molybdenum; D, β -carotene (15 mg), vitamin E (30 mg), and selenium (50 μ g). Groups were as follows: AB, AC, AD, BC, BD, CD, ABCD, or placebo.

^b Estimated from incidence data. NS, nonsignificant.

carcinogenesis provide additional support to this conclusion. There is limited evidence that α -carotene has cancer-preventive activity in single studies of models of liver, lung, skin, and colon carcinogenesis. There is limited evidence that lycopene has cancer-preventive activity in models of colon, liver, mammary gland, and lung carcinogenesis. There is limited evidence that lutein has cancer-preventive activity in experimental models of colon and skin carcinogenesis. There is limited evidence that fucoxanthin has cancer-preventive activity in models of skin and duodenal carcinogenesis.

The discrepancies between experimental and human observations and the findings from the intervention trials greatly complicate the interpretation of data on the effects of β -caro-

tene. Understanding the discrepancies in findings regarding the potential cancer-preventive effects of β -carotene is an important area for future research. Such investigation is also likely to give insight into the process of carcinogenesis. Other carotenoids, canthaxanthin, α -carotene, lutein, lycopene and β -cryptoxanthin, have been investigated less extensively than β -carotene.

Pending further research into their cancer-preventive activity, supplemental β -carotene, canthaxanthin, α -carotene, lutein, and lycopene should not be recommended for cancer prevention in the general population. It should not be assumed that the protective effects of diets rich in carotenoid-containing fruits and vegetables are due to any individual carotenoid.

Appendix

The members of the Working Group of experts were J. A. Baron (Meeting Chairman, Dartmouth Medical School, Lebanon, NH), J. S. Bertram (Cancer Research Center of Hawaii, Honolulu, HI), G. Britton (University of Liverpool, Liverpool, United Kingdom), E. Buiatti (Centro di Documentazione per la Salute, Bologna, Italy), S. De Flora (Institute of Hygiene and Preventive Medicine, Genoa, Italy), V. J. Feron (TNO-Nutrition and Food Research Institute, Zeist, the Netherlands), M. Gerber (Center Val d'Aurelle, Montpellier, France), E. R. Greenberg (Norris Cotton Cancer Center, Lebanon, NH), R. J. Kavlock (United States Environmental Protection Agency, Research Triangle Park, NC), P. Knekt (National Public Health Institute, Helsinki, Finland), W. Malone (National Cancer Institute, Bethesda, MD), S. T. Mayne (Yale University, New Haven, CT), H. Nishino (Kyoto Prefectural University of Medicine, Kyoto, Japan), J. A. Olson (Iowa State University, Ames, IA), H. Pfander (University of Bern, Bern, Switzerland), W. Stahl (Heinrich-Heine University, Dusseldorf, Germany), D. I. Thurnham (Vice-Chairman of the meeting, University of Ulster, Uster, Northern Ireland), J. Virtamo (National Public Health Institute, Helsinki, Finland), and R. G. Ziegler (National Cancer Institute, Bethesda, MD).

The meeting observers were P. Astorg (Institut National de Recherche Agronomique, Dijon, France), R. Goralczyk (Hoffmann-LaRoche Ltd., Basel, Switzerland), R. M. Salkeld (Hoffmann-LaRoche Ltd., Basel, Switzerland), and J. F. Steghens (Hôpital Edouard Herriot, Lyon, France).

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