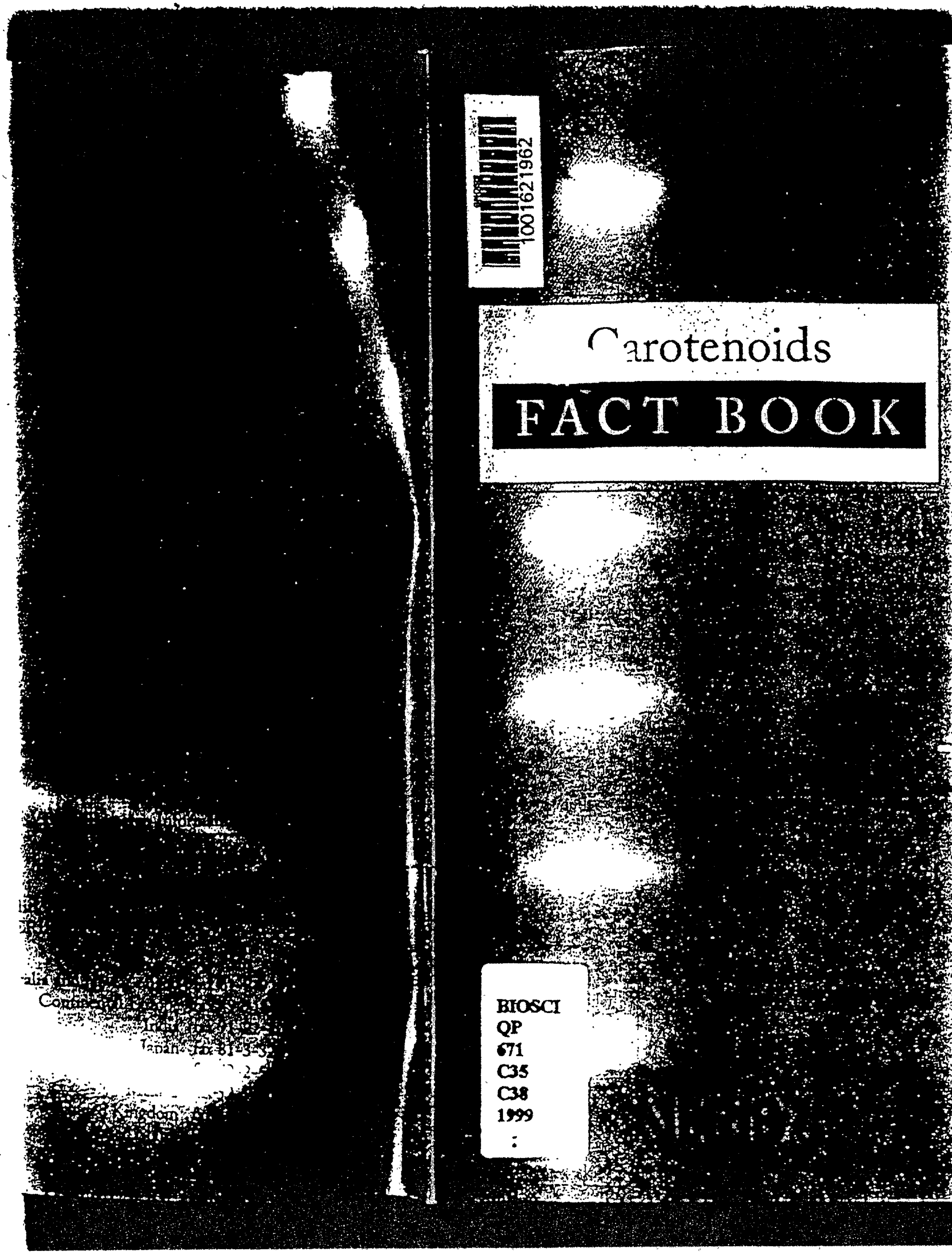
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Introduction

Carotenoids and other antioxidant nutrients are receiving considerable public attention. Recent scientific data suggest that optimal intake of carotenoids and other antioxidants can help delay or prevent the onset of cancer, atherosclerosis, cataracts, macular degeneration and other major degenerative diseases. Such diseases have been linked to damage from free radicals. Free radicals originate in body processes. They also result from environmental exposures, and serve necessary functions in the body. Free radicals are held in check by antioxidants. As long as antioxidants and free radicals are in balance in the body, free radicals do not present a problem. However, when free radical levels increase because of diet, lifestyle, environment or other influences, antioxidant protection is overwhelmed and free radical damage occurs.

Antioxidants play a significant role in the body's defense against excess levels of free radicals and the damage they can cause. These antioxidants include carotenoids, the enzymes superoxide dismutase, catalase and selenium-containing glutathione peroxidase, vitamins C and E, alpha-lipoic acid, and bioflavonoids such as are present in Pycnogenol® brand French maritime pine bark extract.

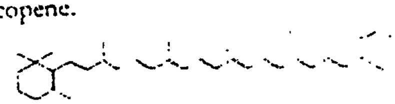
The information that follows offers an overview of carotenoids.

Carotenoids: What they are and what they do

What are carotenoids?

Carotenoids are naturally-occurring colorful compounds that are abundant as pigments in plants. Between 500 and 600 specific carotenoids have been identified. However, only a small number of carotenoids are found in appreciable quantities in human blood and tissues. The major ones are alpha-carotene, beta-carotene, lutein, zeaxanthin, cryptoxanthin and lycopene.

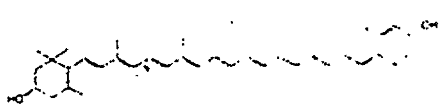
Alpha-Carotene



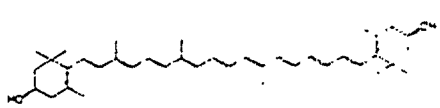
Beta-Carotene (all-trans)

Beta-Carotene (9-cis)

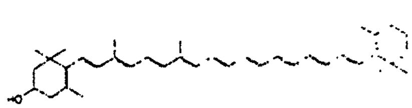
Lutein



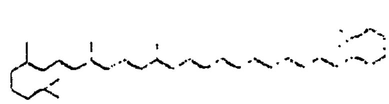
Zeaxanthin



Cryptoxanthin



Lycopene



Is there a difference between supplements of natur mixed carotenoids and synthetic beta-carotene?

Natural mixed carotenoid supplements contain a variety of carotenoids—including alpha- and beta-carotene, lycopene, zeaxanthin, cryptoxanthin and lutein—that are naturally foun various fruits and in yellow and dark green vegetables. Synthe carotenoid supplements contain only beta-carotene. In additic synthetic beta-carotene is composed of all-trans isomers while beta-carotene from algae and in many fruits and vegetables is composed of all-trans, 9-cis and other cis isomers. Research results suggest that 9-cis beta-carotene is a more efficient antioxidant than all-trans beta-carotene. In healthy volunteer. serum levels of lipid peroxidation products were much higher subjects supplemented with synthetic beta-carotene than in subjects supplemented with beta-carotene and other caroteno from natural sources.[1] Results of another study in healthy volunteers showed a preferential uptake of lutein and zeaxant compared to all-trans beta-carotene following supplementati with natural mixed carotenoids.[2]

How do carotenoids work?

Carotenoids function together as a team. They have divers biological functions, and despite the similarities in structur play different roles. Certain carotenoids are precursors of vitamin A and can be metabolically converted into vitamin in the body. Beta-carotene has the highest potential vitam activity. Other provitamin A carotenoids include alpha-carotene and beta-cryptoxanthin.

Carotenoids also have a number of other functions that are completely independent of their potential vitamin A role, i which they function in their naturally-occurring carotenoi forms rather than as vitamin A.

Carotenoids are effective quenchers of singlet oxygen, with lycopene exhibiting the highest singlet oxygen quenching activity. Carotenoids function as chain-breaking antioxidan protecting cells and other body components from free radi attack. Oxidative damage resulting from free radical attack been linked to the onset of premature aging, cancer, atherosclerosis, cataracts, age-related macular degeneration an array of degenerative diseases.

Carotenoids enhance the immune response. In animals, carotenoids stimulate a number of indices of immune func Studies in humans have also shown enhancement of immu parameters by carotenoids.

Carotenoids protect the skin from redness and damage following exposure to UV radiation. Human studies have shown that beta-carotene supplementation combined with topical sunscreens protected the skin from harmful effects of UV radiation and that beta-carotene was protective against UV-induced suppression of immune response.

Lutein and zeaxanthin are the only carotenoids present in the macular region of the retina and are linked to normal function of the macula, which is responsible for sharp and detailed vision. These carotenoids are believed to serve as filters for harmful blue light in the macula and as scavengers of singlet oxygen in retinal tissues.

Certain carotenoids (including lycopene and beta-carotene) have the ability to increase communication between cells by enhancing the exchange of growth regulatory signals. Increased communication between normal cells and cells which have been damaged by chemical carcinogens prevents these damaged cells from becoming malignant.

Carotenoids have been shown to inhibit proliferation of various types of cancer cells. In different cell lines, different carotenoids are more effective in tumor suppression. Specific carotenoids have also been found to be protective against specific cancer types in animal and human epidemiologic studies. For example, decreased risk of various cancers is associated with certain carotenoids: lycopene with prostate cancer; lutein, zeaxanthin, alpha-carotene and beta-carotene with lung cancer; beta-carotene with oral cancers, and cryptoxanthin with cervical cancer.

Based on the diverse and important functions of the major carotenoids—individually or in combination—in protecting the body from damage and disease, intake of a mixture of these carotenoids naturally present in fruits and vegetables is required for good health.

How do carotenoids function as antioxidants?

A number of carotenoids are effective in preventing or controlling free radical generation. Carotenoids are potent quenchers of singlet oxygen, a highly reactive oxygen species that can initiate a chain reaction. Carotenoids also function as chain-breaking antioxidants, especially at low partial pressures of oxygen. Thus, a number of carotenoids can work together to prevent generation of free radicals and can also quench free radical reactions and limit free radical/oxidative damage.

Free radicals are produced as byproducts of metabolic processes and originate from environmental pollutants (such . nitrogen dioxide and ozone of polluted air, heavy metals, halogenated hydrocarbons, ionizing radiation and cigarette smoke). If unchecked by an antioxidant, the highly reactive free radicals attack the cell walls and cell constituents, including DNA, protein and other opportune targets, particularly those containing polyunsaturated fatty acids (PUFAs). When free radicals react with PUFAs, chain reactions generate free radicals in profusion. Free radicals can damage both the structure and function of cell membranes, nucleic acids and electron-dense regions of proteins. This ca result in:

- Cell death or alteration of the cell's response to hormones and neurotransmitters
- Mutations that may be carcinogenic
- Inactivation of enzymes and other proteins

Are carotenoids "typical" vitamins?

Approximately 60 carotenoids have provitamin A activity, of which beta-carotene has the highest potential vitamin A activity. Beta-carotene and other provitamin A carotenoids a safe sources of vitamin A as they are converted to vitamin A only as needed by the body to meet requirements. Since othe biological roles of carotenoids, including their antioxidant functions, are completely independent of provitamin A activity, requirements for and utilization of carotenoids vary according to an individual's oxidative stress status. Concentrations of free radicals, other oxidants, and the polyunsaturated fatty acid content of body tissues are major determinants of oxidative stress status. Effects of carotenoids and other antioxidants usually reduce damage that develops over a long time—typically decades—and have been linked t a reduction in the risk of degenerative diseases such as cance atherosclerosis and other forms of heart disease.

Clinical conditions in which free radicals are thought to be involved

Following is a listing of scores of conditions to which free radicals have been linked.[1] Most likely, free radicals will be the sole cause of only a few. However, free radicals may predispose the human body to a disease that is directly caused by other factors; that is, they may make some conditions worse and may be an antagonist to the body's natural healing processes. In these cases, antioxidants would be useful as adjunct therapy.

Free radical-related conditions:

Primary single organ involvement

Heart and cardiovascular system

Alcohol cardiomyopathy
Keshan disease (selenium deficiency)
Atherosclerosis
Doxorubicin toxicity
Peripheral circulation problems
Stroke

Brain

Hyperbaric oxygen
Neurotoxins
Alzheimer's disease
Senile dementia
Parkinson's disease-MPTP
Hypertensive cerebrovascular injury; cerebral trauma
Neuronal ceroid lipofuscinoses
Allergic encephalomyelitis and other demyelinating diseases
Ataxia-telangiectasia syndrome
Potentiation of traumatic injury
Aluminum overload

Lung

Cigarette-smoke effects
Emphysema
Hyperoxia
Bronchopulmonary dysplasia
Oxidant pollutants
Acute respiratory distress syndrome
Mineral dust pneumoconiosis
Bleomycin toxicity
Paraquat toxicity

Skin

Solar radiation
Thermal injury
Porphyria
Contact dermatitis
Photosensitive dyes
Bloom' syndrome

Eye

Cataractogenesis
Age-related macular degeneration
Ocular hemorrhage
Degenerative retinal damage
Retinopathy of prematurity
Photic retinopathy

Joint abnormalities

Rheumatoid arthritis

Gastrointestinal tract

Endotoxin liver injury
Carbon tetrachloride liver injury
Diabetogenic action of alloxan
Free fatty acid-induced pancreatitis
Nonsteroidal antiinflammatory drug-induced lesions
Abetalipoproteinemia

Kidney

Nephrotic antiglomerular basement membrane disease
Aminoglycoside nephrotoxicity
Heavy metal nephrotoxicity
Renal graft rejection

Erythrocytes

Lead poisoning
Protoporphyrin photooxidation

Malaria
Sickle-cell anemia
Favism
Fanconi anemia

Multiorgan involvement

Cancer

Aging

Disorders of "premature aging"
Immune deficiency of aging

Inflammatory-immune injury

Glomerulonephritis (idiopathic, membranous)
Vasculitis (hepatitis B virus, drugs)
Autoimmune diseases

Ischemia-reflow states

Drug and toxin-induced reactions

Iron overload

Idiopathic hemochromatosis
Dietary iron overload
Thalassemia and other chronic anemias

Nutritional deficiencies

Kwashiorkor
Vitamin E deficiency

Alcohol damage

Radiation injury

Amyloid diseases

Carotenoids: Sources, requirements and safe

Are carotenoids considered essential to human healt

Carotenoids have not been officially recognized as essential nutrients. Provitamin A carotenoids can be converted in the body to vitamin A, which is recognized as an essential nutrient, and can help to prevent or cure rapidly-developing symptoms of overt vitamin A deficiency. Beta-carotene supplementation had a therapeutically similar effect to vitamin A palmitate in treatment of vitamin A deficiency in study of 510 children in Senegal.[4]

Vitamin A status was improved by intake of a beta-carotene-containing wafer, but not by intake of a similar amount of be carotene from dark green leafy vegetables in Indonesian women who were anemic and had low vitamin A status.[5] In a study of anemic school children in Indonesia, fruit was approximately twice as effective as vegetables in increasing serum vitamin A levels.[6]

Is there an officially recommended dietary intake for carotenoids?

At the present time, there is no officially recommended diet intake for carotenoids. The recommended dietary intake for vitamin A is 1,000 retinol equivalents (RE) for men and 80(for women. The conversion factor is as follows:[7]

1 RE = 1 mcg retinol
= 6 mcg beta-carotene
= 12 mcg other provitamin A carotenoids

As evidence continues to accumulate on protective effects of carotenoids in human health, a specific recommended dietar intake for carotenoids separate from vitamin A may be considered. Based on dietary guidelines of governmental agencies for optimal intakes of fruits and vegetables to help prevent chronic disease, it appears that a daily intake of 6 m beta-carotene could be achieved. The Alliance for Aging Research, a U.S. Citizen advocacy organization for research improve the health and independence of older people, has recommended 10 to 30 mg beta-carotene per day for optim health.

What are the dietary sources of carotenoids?

The richest dietary sources of carotenoids are fruits and vegetables. In general, the estimated daily intake supplied by the "normal" diet ranges from 1.5-3 mg for beta-carotene and from 3.6-7.6 mg for total carotenoids. In a recent survey in the United States (CSFII), average dietary intake of beta-carotene was approximately 1.4 mg and of total carotenoids was approximately 7.6 mg.

Typical Carotenoid Content of Selected Fruits and Vegetables[8]
(mcg /100 g portion)

Fruits and Vegetables	Beta-carotene	Alpha-carotene	Lutein & zeaxanthin	Lycopene	Cryptoxanthin
Apples, raw		30			
Apricots, canned, drained	6,640	0	0	65	0
Apricots, raw	2,554	0	0	5	0
Asparagus, raw	493	12			
Avocados, raw	53	28			36
Bananas, raw	21	5	0	0	0
Beet greens, cooked, drained	2,560				
Blueberries, raw	35	0			
Broccoli, cooked, drained	1,042	0	2,226	0	0
Brussels sprouts, cooked, drained	465	0	1,290	0	0
Cabbage, cooked, drained	90				
Cabbage, raw	65	0	310	0	0
Cantaloupe, raw	1,595	27	40	0	0

Typical Carotenoid Content of Selected Fruits and Vegetables[8]
(mcg /100 g portion)

Fruits and Vegetables	Beta-carotene	Alpha-carotene	Lutein & zeaxanthin	Lycopene	Cryptoxanthin
Carrots, cooked, drained	8,015	4,109			
Carrots, raw	8,836	4,649			
Celery, raw	150	0	232	0	0
Corn, yellow, canned, drained	30	33	884	0	0
Cucumber, peeled, raw	31	8			
Grapefruit, pink, raw	603	5	13	1,462	12
Grapefruit, white, raw	14	8			
Grapes, red or green	39				
Green beans, cooked, drained	552	92	700	0	0
Greens, collard, cooked, drained	4,418	90	8,091	0	20
Greens, turnip, cooked, drained	4,575	0	8,440	0	0
Kale, cooked, drained	6,202	0	15,798	0	0
Lettuce, iceberg, raw	192	2	352	0	0
Lettuce, romaine, raw	1,272	0	2,635	0	0
Mangos, raw	445	17			11
Nectarines, raw	101	0			59
Okra, raw	432	28			
Onions, spring, raw	391	6			

Typical Carotenoid Content of Selected Fruits and Vegetables[8]
(mcg/100 g portion)

Fruits and Vegetables	Beta-carotene	Alpha-carotene	Lutein & zeaxanthin	Lycopene	Cryptoxanthin
Orange juice, fresh	4	2	36		15
Oranges, raw	51	16	187	0	122
Papayas, raw	276	0	75	0	761
Peaches, canned, drained	334	0	33	0	141
Peaches, raw	97	1	57	0	24
Pears, canned, drained	4				
Pears, raw	27	6			
Peas, green, canned, drained	320	0	1,350	0	0
Peas, green, frozen	320	33			
Peppers, green, raw	198	22			
Peppers, red, raw	2,379	59			2,205
Peppers, yellow, raw	120				
Pineapple, canned, drained	30				
Plums, raw	98				16
Potato, sweet, baked	9,488	0	0	0	0
Potato, white, raw	6				
Pumpkin, canned	6,940	4,795	0	0	0
Raspberries, raw	8	12			0

Typical Carotenoid Content of Selected Fruits and Vegetables[8]
(mcg /100 g portion)

Fruits and Vegetables	Beta-carotene	Alpha-carotene	Lutein & zeaxanthin	Lycopene	Cryptoxanthin
Spinach, cooked, drained	5,242	0	7,043	0	0
Spinach, raw	5,597	0	11,938	0	0
Squash, acorn, cooked	490	0	66	0	0
Squash, butternut, baked	4,570	1,130			
Squash, zucchini, raw	410	0	2,125	0	0
Strawberries, raw		5			
Tangerines, raw	71	14	243	0	485
Tomato juice, canned	428	0	60	9,318	0
Tomatoes, red, cooked	300	0	150	4,400	0
Tomatoes, red, raw	393	112	130	3,025	0
Watermelon, raw	295	0	17	4,868	103

Blank values indicate unreported data.

How much carotenoid activity is lost during the handling, storage and processing of foods?

Factors influencing carotenoid levels in foods include varietal differences, variable growth and harvesting conditions and different postharvest handling and processing methods. Carotenoids are degraded by light in the presence of oxygen. Changes in carotenoid content following cooking can vary, depending on the specific carotenoid and the method of cooking. Mild cooking of food before ingestion generally improves the bioavailability of carotenoids. [7-12]

What quantity of carotenoids does an individual need?

This question is incomplete unless one adds: "to do what?"

- To prevent vitamin A deficiency?
- To prevent oxidation of lipids, prevent free radical damage and promote optimal health?
- To produce a therapeutic effect?

If prevention of vitamin A deficiency is the objective, quantities of provitamin A carotenoids to meet the RDA for vitamin A are adequate for most individuals in developed countries. If prevention of oxidative damage and promotion of optimal health is the objective, higher intakes of carotenoids are necessary.

Does the average diet supply optimal amounts of carotenoids?

Research data show that considerably higher intakes of carotenoids and other antioxidants than are consumed in the average diet are necessary to prevent free radical cell damage that compromises health. Although governmental agencies recommend at least five servings of fruits and vegetables per day, many individuals consume far less than the recommended number of servings. Based on the CSFII survey in the United States, 85% of Americans don't meet both USDA fruit and vegetable recommendations on a daily basis and 60% of Americans don't reach the "5 a day" minimum for fruits and vegetables combined.

However, depending on selection of specific fruits and vegetables, intake of beta-carotene and other carotenoids may be higher than the average or may be lower, even for individuals who regularly consume at least five servings of fruits and vegetables per day. For example, a diet that includes broccoli, carrots, tomato juice, watermelon and pink grapefruit provides over 11 mg beta-carotene and over 20 mg of other major carotenoids. In contrast, a diet that includes corn, green beans, white potato, an apple and a pear provides less than 1 mg beta-carotene, less than 2 mg alpha-carotene, 2-3 mg lutein and zeaxanthin and no lycopene or cryptoxanthin and is far below the level recommended by governmental agencies or The Alliance for Aging Research. Thus, the source as well as the quantity of fruits and vegetables eaten daily must be considered when evaluating the adequacy of total carotenoid intake.

What evidence suggests that people aren't getting enough carotenoids from their diets?

The majority of research evidence to date shows that individuals with low carotenoid intakes or low blood carotenoid levels have increased risk for development of a number of degenerative diseases and conditions. Epidemiologic studies have provided consistent positive results for high intakes of carotenoid-rich fruits and vegetables or high carotenoid blood levels and decreased disease risk. Although fruits and vegetables contain a large number of carotenoids, only six major carotenoids are presently considered important for human health. In the past, most of the research activity focused on beta-carotene due to its provitamin A activity. Results of intervention trials using synthetic beta-carotene supplements have been generally neutral or negative, with some positive results. In contrast, studies of other specific carotenoids or mixed carotenoids have provided interesting, generally positive results. Thus, based on current research data, increased intake of a mixture of natural carotenoids, rather than beta-carotene alone, may be of greater benefit in disease prevention.

• Cancer

Epidemiologic Studies

Data from numerous epidemiologic studies have shown that individuals with the highest intakes of carotenoid-rich fruits and vegetables and/or high blood levels of specific carotenoids usually have the lowest risk for certain types of cancer. (See Table on Epidemiologic Studies of Carotenoid Levels and Cancer Risk for more detailed data)

In one study of cervical cancer, blood beta-carotene levels were lower in cancer cases.[13] In another study, serum levels of total carotenoids, cryptoxanthin and alpha-carotene were lower in cancer patients than in controls.[14] Beta-carotene concentrations in plasma and cervical tissue were lower in patients with cervical cancer or precancer compared to controls.[15] Serum carotenoid levels were not associated with cancer risk in a study of patients with ovarian cancer.[16] Increased dietary beta-carotene intake was associated with a decreased risk of endometrial cancer.[17]

Beta-carotene blood levels were lower in a group of postmenopausal women with breast cancer,[18] and dietary beta-carotene intake was inversely associated with cancer risk in another study of breast cancer.[19] In a study of premenopausal women, breast cancer risk in the highest quartile of intake was 33% lower for alpha-carotene, 54% lower for beta-carotene and 53% lower for lutein plus zeaxanthin compared to the lowest quartile.[20] Increased intake of alpha-carotene, beta-carotene and lutein/zeaxanthin was associated with decreased breast cancer risk in premenopausal women with a family history of breast cancer.[21] Increased reported intake of beta-carotene was associated with a decreased risk of breast cancer among postmenopausal women. Beta-carotene intake was inversely related to breast cancer risk for the time period 20 years prior to the reference date.[22] In another study, serum lycopene levels were inversely associated with breast cancer risk.[23] Serum beta-carotene and vitamin A levels were lower in patients with epithelial cancer than in controls.[24]

An increased intake of fruits and vegetables was associated with a decreased risk of cancer of the mouth and pharynx.[25] In another study, increased intake of beta-carotene was associated with a decreased risk of a second primary tumor in patients with cancer of the oral cavity, pharynx or larynx.[26] Risk of stomach cancer was decreased with increasing carotene intake.[27] Intake of tomatoes, which are high in lycopene, was lower in patients with digestive tract cancer than in controls.[28]

In a study of the association between serum beta-carotene levels and risk of lung, bladder and gastrointestinal cancer, risk of lung cancer was higher in men with serum beta-carotene levels in the lowest quintile.[29] Blood beta-carotene levels were also lower in a group of patients with lung and stomach cancers.[30] In a study of nine primary sites, high serum beta-carotene levels were protective against lung cancer.[31]

A number of studies have investigated the association between carotenoid levels and risk of lung cancer. In one study, increased dietary carotene intake was associated with a decreased lung cancer risk.[12] In another study, there was a dose-dependent inverse relationship between dietary intake of alpha-carotene, beta-carotene and lutein and risk of lung cancer.[13] Serum beta-carotene levels were lower in lung cancer patients than in controls.[14] There was an inverse association between dietary beta-carotene intake and lung cancer risk in nonsmokers but the inverse association was greater for total carotenoid intake than for beta-carotene alone.[15] Other study results showed that dietary beta-carotene intake was associated with reduced lung cancer risk[36] and that serum total carotenoid and beta-carotene levels were lower in patients with lung cancer.[37]

Lung cancer risk was increased for men in the lowest quintile of serum beta-carotene levels and dietary intakes.[38,39] Serum carotenoid levels were also lower in a group of lung cancer patients.[40] Increased intake of carotenoid-rich fruits and vegetables was associated with decreased risk of lung cancer.[41,42] Lung cancer risk was 57% lower in subjects with carotenoid intakes in the highest quartile compared to the lowest quartile.[43] In contrast, dietary carotenoid intake was not associated with lung cancer risk in another study.[44] In a group of nonsmokers, carotenoid intakes in the lowest tertile were associated with increased lung cancer risk.[45] Results of another study showed a relationship between low dietary intakes of fruits and vegetables, alpha-carotene, beta-carotene and lutein-zeaxanthin and increased risk of lung cancer.[46] Intake of alpha-carotene, but not beta-carotene, was inversely associated with lung cancer risk in a study of men.[47]

Risk of thyroid cancer was decreased by 42% in the highest quartile of beta-carotene intake.[48] Risk of prostate cancer decreased with increased dietary intake of lycopene but not other carotenoids.[49] In studies that evaluated the association between carotenoids and risk of cancers of all sites, serum beta-carotene levels were lower in cancer cases in one study. There was no association between plasma alpha- and beta-carotene levels and prostate cancer mortality.[51] Low plasma carotene levels were associated with an increased risk of cancer of the colon and lung.[52]

Epidemiologic Studies of Carotenoid Levels & Cancer Risk

Cancer Site	Study Location	Number of Cancer Cases	Study Findings	Date Reference
Cervix	United States	116	Beta-carotene blood levels were lower in cancer cases	(1991) Palan
Cervix	United States	50	Serum levels of total carotenoids, cryptoxanthin and alpha-carotene were lower in cancer cases	(1993) Batieha

Epidemiologic Studies of Carotenoid Levels & Cancer Risk

Cancer Site	Study Location	Number of Cancer Cases	Study Findings	Date/ Reference
Cervix	United States	60	Beta-carotene levels in plasma and cervical tissue were lower in cancer and precancer cases	(1995) Peng[15]
Ovaries	United States	35	Serum carotenoid levels were not associated with cancer risk	(1996) Helzlsouer[16]
Endometrium	Switzerland, Italy	368	Increased dietary beta-carotene intake was associated with decreased cancer risk	(1996) Negri[17]
Breast	United States	83	Beta-carotene blood levels were lower in postmenopausal women with cancer	(1990) Potischman[18]
Breast	Italy	2,569	Inverse association between dietary beta-carotene intake and cancer risk	(1996) Negri[19]
Breast	United States	297	Cancer risk in highest quartile of intake was 33% lower for alpha-carotene, 54% lower for beta-carotene and 53% lower for lutein and zeaxanthin	(1996) Freudenheim[20]
Breast	United States	2,697	Increased intake of alpha- and beta-carotene and lutein/ zeaxanthin was associated with decreased cancer risk in premenopausal women with a family history of breast cancer	(1999) Zhang[21]
Breast	Sweden	273	Inverse association between dietary beta-carotene intake and cancer risk	(1999) Jumaan[22]

Epidemiologic Studies of Carotenoid Levels & Cancer Risk

Cancer Site	Study Location	Number of Cancer Cases	Study Findings	Date/ Reference
Breast	United States	105	Inverse association between serum lycopene levels and cancer risk	(1998) Dorgan[23]
Epithelium	India	285	Serum beta-carotene and vitamin A levels were lower in cancer cases	(1990) Ramaswamy[24]
Mouth & Pharynx	United States	190	Increased intake of fruits and vegetables was associated with reduced cancer risk	(1990) Gridley[25]
Oral Cavity, Pharynx, Larynx	Italy	380	Decreased risk of second primary tumor with increased beta-carotene intake	(1996) Barbone[26]
Upper Digestive Tract	United States	50	Risk of stomach cancer was decreased with increasing carotene intake	(1995) Zheng[27]
Digestive Tract	Italy	2,706	Intake of tomatoes, which are high in lycopene, was lower in cancer cases	(1994) Franceschi[28]
Lung, Bladder, G.I. Tract	United States	284	3.4-fold risk of lung cancer for men with serum beta-carotene levels in lowest quintile	(1985) Nomura[29]
Lung, Stomach, Colon	Switzerland	129	Blood beta-carotene levels were lower for lung and stomach cancer cases	(1984) Stahelin
9 Primary Sites	United States	436	Serum beta-carotene had a protective association with lung cancer	(1991) Comstock[31]
Lung, Epithelium	United Kingdom	171	Serum beta-carotene levels were lower in cancer cases; increased dietary carotene intake was associated with decreased lung cancer risk	(1991) Harris[32]

Epidemiologic Studies of Carotenoid Levels & Cancer Risk

Cancer Site	Study Location	Number of Cancer Cases	Study Findings	Date/ Reference
Lung	United States	332	Dose-dependent inverse association between cancer risk and dietary intake of beta- and alpha-carotene and lutein but not lycopene or cryptoxanthin	(1993) Le Marchand[33]
Lung	Australia	64	Serum beta-carotene levels were lower in cancer cases	(1989) Kune[34]
Lung	United States	124	Inverse association between cancer risk and dietary beta-carotene intake in nonsmokers; inverse association greater for total carotenoid intake	(1994) Candelora[35]
Lung	United States	413	Dietary beta-carotene intake was associated with reduced cancer risk	(1994) Mayne[36]
Lung, Other Sites	United States	156	Serum total carotenoid and beta-carotene levels were lower in cancer cases	(1989) Connett[37]
Lung, Skin, Other Sites	United Kingdom	271	Cancer risk for subjects in 2 highest quintiles of serum beta-carotene levels was 60% of the risk of men in lowest quintile	(1988) Wald[38]
Lung	Hong Kong	50	3.8-fold increased relative risk for men with beta-carotene intake in lowest quintile	(1988) Ho[39]
Lung	United States	59	Serum carotenoid levels were lower in cancer cases	(1990) Le Gardeur[40]
Lung	United States	839	Increased intake of carotenoid-rich fruits and vegetables was associated with decreased cancer risk	(1990) Jain[41]
Lung	Japan	282	Increased intake of carotenoid-rich fruits and vegetables was associated with decreased cancer risk	(1993) Chang-Ming[42]

Epidemiologic Studies of Carotenoid Levels & Cancer Risk

Cancer Site	Study Location	Number of Cancer Cases	Study Findings	Date/ Reference
Lung	Uruguay	541	57% lower cancer risk in the highest quartile of carotenoid intakes	(1999) DeStefani[43]
Lung	China	965	No association between dietary carotenoid intake and cancer risk	(1990) Wu-Williams[44]
Lung	Finland	117	2.5-fold higher cancer risk in non-smokers with carotenoid intakes in lowest tertile	(1991) Knekt[45]
Lung	United States	1,084	Low dietary intakes of fruits and vegetables, alpha- and beta-carotene and lutein zeaxanthin were associated with increased cancer risk	(1996) Ziegler[46]
Lung	Finland	138	Inverse association between dietary intake of alpha-carotene, but not beta-carotene, and cancer risk	(1999) Knekt[47]
Thyroid	Italy	399	42% decreased cancer risk in the highest quartile of beta-carotene intake	(1997) D'Avanzo[48]
Prostate	United States	812	Dietary intake of lycopene but not other carotenoids was associated with decreased cancer risk	(1995) Giovannucci[49]
All Sites	Turkey	208	Serum beta-carotene levels were lower in cancer cases	(1995) Torun[50]
All Sites	Switzerland	290	No association between plasma alpha- and beta-carotene levels and prostate cancer mortality	(1999) Eichholzer[51]
			Low plasma carotene levels were associated with increased risk of lung and colon cancer	(1996) Eichholzer[52]

Intervention Trials

In a 5-year randomized nutrition intervention trial of 29,584 adults in Linxian, China, there was a significant 9% reduction in risk of overall mortality in the group supplemented with beta-carotene, vitamin E and selenium, which was due primarily to a 13% reduction in cancer risk.[53]

In a clinical trial of 864 patients who had previously had a colorectal adenoma removed, supplementation with beta-carotene or vitamins C and E did not decrease the occurrence of new adenomas over a 4-year period. It was noted that the results are in apparent conflict with a decreased risk of invasive colorectal cancers suggested by epidemiologic studies, which may have detected an effect that occurs only after adenomas develop.[54]

In a primary prevention trial of 29,133 male smokers 50 to 69 years of age from Finland who had smoked an average of 21 cigarettes per day for an average of 36 years (the ATBC Study), the incidence of lung cancer was 18% higher in the group supplemented with 20 mg synthetic beta-carotene per day for 5 to 8 years.[55] This effect may be associated with heavier cigarette smoking and higher intake of alcohol.[56] The incidence of prostate cancer was 23% higher in beta-carotene-supplemented subjects compared to subjects that did not receive beta-carotene, but the difference was not statistically significant.[57]

In another study of high risk subjects that involved 18,314 smokers, former smokers and workers exposed to asbestos in the United States (the CARET Study), the relative risk of lung cancer was 28% higher in the group supplemented with 30 mg synthetic beta-carotene plus 25,000 I.U. vitamin A per day over a 4-year period compared to the group on placebo.[58] However, among former smokers, lung cancer risk in beta-carotene-supplemented subjects was approximately the same as in subjects on placebo. There was also a correlation between alcohol intake and lung cancer risk. The risk for lung cancer was only slightly greater for beta-carotene-supplemented nondrinkers than for subjects on placebo.[59,60]

A trial of 22,071 male physicians 40 to 84 years of age investigated the effect of synthetic beta-carotene (50 mg on alternate days) on the incidence of cancer over an average follow-up period of 12 years. There were virtually no early or late differences in the overall incidence of cancer in the beta-carotene-supplemented group compared to the placebo group.[61]

A limited number of intervention trials in patients with oral leukoplakia (precancerous lesions of the oral cavity) have shown that beta-carotene, alone or in combination with other antioxidants, produces regression of lesions. The beneficial effects are greater in smokers.[62]

• Coronary Heart Disease

Epidemiologic Studies

Results of large epidemiologic studies have shown a correlation between increased intake of carotenoids and decreased risk of coronary heart disease. In a study of 1,899 men with hyperlipidemia over a follow-up period of 13 years in the United States, there was an inverse relationship between serum carotenoid levels and risk of coronary heart disease.[63] Results of a large prospective study of 2,974 middle-aged men in Switzerland showed an increased risk of death from coronary heart disease among those in the lowest quartile of plasma carotene levels.[64]

In an 8-year study of 87,245 healthy women in the United States, women in the highest quintile of beta-carotene intakes had a 22% lower risk of coronary heart disease compared to women in the lowest quintile. After 4 years of follow-up in 39,910 men in the United States, those in the highest quintile of beta-carotene intake were 25% less likely to have suffered a coronary heart disease event.[65]

Results of a study in Italy of 433 women with nonfatal acute myocardial infarction and 869 controls showed an inverse association between nonfatal acute myocardial infarction risk and beta-carotene intake, with a 50% decreased risk for the highest quintile of intake compared to the lowest quintile.[66] In a multicenter study in 10 European countries, there was a significant inverse association between adipose tissue levels of lycopene and risk of first acute myocardial infarction, with a 48% decreased risk in subjects with lycopene levels in the 90th percentile compared to the 10th percentile.[67] A case-control evaluation in the United States of 123 patients with nonfatal myocardial infarction and 246 controls from a group of 25,802 subjects demonstrated a significantly increasing risk for subsequent myocardial infarction with decreasing serum beta-carotene levels in smokers.[68]

In a study of 5,133 adults in Finland who were initially free from heart disease, women with both dietary vitamin E and carotenoid intakes in the highest tertile had an 84% lower risk of coronary heart disease mortality than women with intakes in the lowest tertile. No significant combined effects of vitamin intakes were observed in men.[69]

Intervention Trials

Mortality from cerebrovascular disease was 10% lower among subjects supplemented with beta-carotene, vitamin E and selenium in a randomized intervention trial of 29,584 adults from Linxian, China.[53]

A subgroup analysis of the ATBC trial of male smokers 50-69 years of age studied the frequency of major coronary events in men who had experienced a previous myocardial infarction. There were no significant differences in the number of major coronary events between the beta-carotene-supplemented group (20 mg synthetic beta-carotene per day) and the placebo group but there were significantly more deaths from coronary heart disease in the supplemented group.[70]

In a subgroup analysis of 333 physicians with a history of stable angina pectoris and/or coronary revascularization participating in a trial of 22,071 male physicians in the United States, those on 50 mg beta-carotene on alternating days had a significant 51% reduction in risk of major coronary events. The beneficial effect of beta-carotene first appeared during the second year of supplementation.[65]

• Cataracts and Age-Related Macular Degeneration

Epidemiologic Studies

Epidemiologic studies have also shown an inverse correlation between levels of carotenoids and other antioxidants and risk of cataracts and age-related macular degeneration. In a study of 112 subjects 40-70 years old in the United States, high plasma levels of at least two of three antioxidants (carotenoids, vitamin C and vitamin E) were associated with a significantly decreased risk of cataract development.[71] Serum carotenoids

were not significantly associated with cataract risk in a random sample of 400 adults 50-86 years old in the Beaver Dam Eye Study in the United States. However, there were marginal inverse associations of cataract risk with serum lutein and cryptoxanthin levels in people 65 years of age and older.[72] The odds ratio for senile cataract risk was 2.6 for patients with serum beta-carotene and vitamin E levels in the lowest third in a 15-year study in Finland of 47 patients with cataracts and 94 controls.[73]

In an evaluation of 334 subjects who participated in the Beaver Dam Eye Study in the United States, individuals with serum lycopene levels in the lowest quintile were twice as likely to have age-related macular degeneration.[74] Results of a study of 3,654 subjects in Australia showed no significant association between age-related macular degeneration and intake of carotene.[75]

The risk of age-related macular degeneration in subjects with high serum carotenoid levels was one-third that of subjects with low levels in a study in the United States of 421 patients with age-related macular degeneration and 615 controls.[76]

In a Multicenter Eye Disease Case-Control Study in the United States, individuals in the highest quintile of dietary carotenoid intake had a 43% lower risk for age-related macular degeneration compared with individuals in the lowest quintile. Zeaxanthin and lutein were the carotenoids most strongly associated with a decreased risk.[77]

Intervention Trials

In a multicenter trial in the United States of the effects of daily supplementation with beta-carotene, vitamin C, vitamin E and selenium on progression of age-related macular degeneration, distance visual acuity stabilized over 18 months in the supplemented group but declined in the placebo group.[78] Results of the ATBC study in Finland did not show a beneficial effect of beta-carotene and vitamin E supplements on the risk of age-related macular degeneration.[79]

In conclusion, the majority of the cited epidemiologic studies have linked lower levels of carotenoids with increased risk of degenerative diseases, or conversely, have shown that increased carotene intakes or blood levels are associated with decreased risk of disease. The specific carotenoids that were protective varied for different conditions. In some cases, an individual carotenoid was protective; in other situations, it was a mixture of carotenoids that was beneficial. Results of intervention trials utilizing beta-carotene supplements only were not as positive. Future trials on carotenoids will hopefully focus on a mixture of carotenoids to further evaluate their role in disease prevention. Based on results to date, a number of researchers have recommended increased intakes of carotenoids and other antioxidants to provide adequate protection against present-day environmental stresses.

What factors determine an individual's oxidative stress status and antioxidant requirement?

The requirement for antioxidants varies from individual to individual—with the level and nature of activity, diet, exposure to psychological stress and polluted environments. In addition, persons who have certain medical conditions, who are taking medications, who smoke, drink alcohol and/or who are exposed to radiation from the sun may have increased requirements for carotenoids and other antioxidants.

The level of carotenoids and other antioxidants an individual needs can only be approximated by reviewing his or her exposure to various risk factors. A definitive profile of oxidative stress status must be determined by laboratory testing.

Can carotenoids and other antioxidants reverse degenerative disease associated with free radical damage?

No. Antioxidants act as long-term preventive agents. They cannot reverse damage, but can retard its progress. Damage that leads to chronic diseases is cumulative, usually occurring over decades. It is important that antioxidant requirements be met on a daily basis to slow this cumulative damage that builds up over the course of a lifetime.

Safety of carotenoids: Are increased intakes of carotenoids safe?

The conversion of beta-carotene and other provitamin A carotenoids are regulated by the vitamin A status of an individual. Thus, high intakes of carotenoids do not lead to

abnormally elevated blood vitamin A levels or to symptoms of hypervitaminosis A.

The majority of available data on safety of carotenoids is for beta-carotene. Toxicity studies in animals have demonstrated that beta-carotene is not carcinogenic, mutagenic or teratogenic. Doses of 20 to 180 mg beta-carotene per day for many years have been used to treat erythropoietic protoporphyria, with no evidence of toxicity and without development of abnormally-elevated blood vitamin A levels.[20]

However, in two intervention trials of synthetic beta-carotene supplementation in high risk groups (29,133 male smokers for 5 to 8 years, and 18,314 smokers, former smokers and workers exposed to asbestos over an average follow-up of 4 years), risk of lung cancer and overall mortality rate was increased in the beta-carotene-supplemented group compared to the group on placebo.[22,23] In contrast, an intervention trial of 22,071 male physicians for 12 years showed no significant differences in incidence of lung cancer or cardiovascular disease or overall mortality rate in the beta-carotene-supplemented group compared to the placebo group.[24] It has been suggested that reversal of lifelong risk factors may require longer periods of time to account for latent periods of cancers. In addition, these studies evaluated synthetic beta-carotene, rather than a mix of natural carotenoids that are present in fruits and vegetables.

What are the primary raw materials from which carotenoid supplements are made?

Natural mixed carotenoids are isolated from algae or palm oil. Synthetic beta-carotene is produced from chemicals. Lycopene is extracted from tomatoes, from a fermentation process or is produced by chemical synthesis. Lutein is extracted from marigold flowers, but is also available at lower concentrations in some fruits and vegetables. Zeaxanthin is isolated from algae. Alpha-carotene is present with other carotenoids in algae or palm oil. Cryptoxanthin is isolated from citrus and tropical fruits.

On taking carotenoids

What are the potential benefits of carotenoids?

An adequate supply of carotenoids and other antioxidants protects the integrity of the body's cells and may lower one's risks of developing degenerative diseases that can result from oxidative/free radical damage. Free radicals are normal byproducts of cell activity and serve necessary and desirable functions in the body. However, an overload of free radicals resulting from certain lifestyle and dietary habits, medical conditions and environmental exposures can damage cells and increase an individual's risk of disease. Free radical-induced cell damage has been linked in research studies to:

- A variety of cancers
- Coronary heart disease
- Premature aging
- Cataract formation
- Age-related macular degeneration

In addition, research suggests that carotenoids:

- Enhance the action of the immune system
- Are effective in treatment of erythropoietic protoporphyria, an inherited light-sensitive skin disorder
- Activate expression of genes involved in cell-to-cell communication
- Protect the skin from UV radiation.

Does optimal intake of carotenoids and other antioxidants ensure good health?

Optimal nutrition can reduce the risk of disease, but nothing can guarantee good health because about half of an individual's risk of developing a disease like heart disease or cancer is influenced by genetic factors. However, a number of factors that influence health are under the control of the individual: they depend on lifestyle and exposure to risk factors. If a

person minimizes the risk by avoiding things known to be bad for health (smoking, heavy drinking, exposure to chemical pollutants) and taking advantage of things that are good (pursuing moderate exercise, getting adequate nutrients), he or she increases the odds that his or her quality of life in later years will be good.

What kind of results can be expected from regular, adequate intake of carotenoids and other antioxidants?

The important effects of carotenoids and other antioxidants are not readily observable. The person who takes adequate amounts of carotenoids most likely will not see or feel a short-term difference.

Because major effects of carotenoids and other antioxidants take place at the cellular level, evidence of bolstered protection requires testing for plasma antioxidant levels and for markers of cell damage. The benefits of adequate intake of carotenoids and other antioxidants only become apparent in the long term, when reduction in oxidative damage results in lowered incidence and severity of chronic diseases.

Is it better to get carotenoids from dietary intake rather than from a supplement?

Dietary sources of micronutrients are generally regarded as being preferable to supplements because foods contain complex mixtures of ingredients, the actions and interactions of which are not fully understood but which may be beneficial. Supplements, even natural ones, most likely do not contain all of the components found in a range of foods. The best approach is to get as many nutrients as possible from the diet (at least 5 portions per day of fruits and vegetables) and make up any deficits by using natural supplements. It has been shown that the bioavailability of carotenoids from supplements is higher than from fruits and vegetables.

For persons who opt for carotenoid supplementation, at what time of life would it be most beneficial? Should carotenoids be taken on a regular schedule or only during periods of heavy oxidative stress?

There are no definitive data on when supplementation of carotenoids and other antioxidants should begin, although some researchers are finding free radical-induced disease in children. Until further evidence is in, it is probably prudent to begin supplementation in young adulthood and continue throughout one's life.

It should also be noted that it takes time to build up carotenoid levels. To increase intake of carotenoids only at the time of high oxidative stress would very likely not produce optimal protection.

What forms and dosages of carotenoid supplements are available?

In the United States, carotenoid supplements are available in 6 mg and 15 mg soft gelatin capsules, 2-piece capsules and/or powdered tablets. Carotenoids are also included in multivitamins.

Should carotenoids be taken in a single dose each day?

Taking carotenoids more than once a day will usually increase the body's utilization of the supplement. And because carotenoids are fat-soluble, carotenoid supplements are absorbed better when taken with a meal that contains fat.

What about side effects and contraindications?

The only common side effect associated with intake of high levels of carotenoids (30 mg or more per day) from supplements or carotenoid-rich foods is yellowing of the skin. This is a harmless condition that disappears when the carotenoid intake is reduced.[56] In intervention trials in high risk groups (29,133 male smokers for 5 to 8 years and 18,314 smokers, former smokers and workers exposed to asbestos over an average follow-up of 4 years) incidence of lung cancer and overall mortality rate were increased in subjects supplemented with synthetic beta-carotene (20-30 mg per day).[57,58] In another recent intervention trial of 22,071 male physicians, there were no major side effects significantly associated with beta-carotene supplementation (50 mg on alternate days over an average follow-up period of 12 years.)[61]

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Appendix

A brief history of carotenoids

In 1913, E.V. McCollum and Marguerite Davis showed that a fat-soluble factor in butter—later characterized as vitamin A—stimulated the growth of rats fed an incomplete diet. The belief that some colored plant extracts with similar effects, later known as carotenoids, might be biologically converted to vitamin A was confirmed by T. Moore in 1930.

Originally carotenoids were considered important only as precursors of vitamin A. More recently, there has been significant interest in evaluation of carotenoids for roles that are unrelated to their conversion to vitamin A. Although antioxidant properties of beta-carotene were discovered in the late 1960's, the biological significance was not realized until much later. Early interest in carotenoids was motivated in large part by the consistent observation that consumers of fruits and vegetables, particularly dark green and deep yellow vegetables, had a decreased cancer risk.

Beta-carotene was the primary research focus of earlier studies evaluating the role of carotenoids in disease prevention because it was the best known antioxidant of the carotenoids and ...ause of its potential vitamin A activity. In addition, there ...e insufficient data on the food content of other carotenoids ...address their intake in relation to disease. As it became ...own that other carotenoids in addition to beta-carotene have ...nctions that are important in disease prevention, and with ...he availability of data on individual carotenoids, a number of studies have been evaluating the protective effects of various carotenoids, rather than beta-carotene alone. Interesting new health effects have recently been reported for lutein, zeaxanthin and lycopene. Results of ongoing and future studies should provide more specific documentation of levels and combinations of carotenoids that are optimal for disease prevention.

Glossary

Antioxidants: Substances that can prevent or ... of a molecule.

Free radicals: Highly reactive substances that ... internal and external sources. Internally they a... by the immune system (e.g., in the host defens... bacteria), during oxygen metabolism and durin... of lipid peroxidation. External sources include ... ionizing radiation, cigarette smoke, air pollutan... metals, ozone, organic solvents and pesticides.

Lipids: Major water-insoluble biological molecu... include: neutral lipids (fats and oils), phospholip... and waxes.

Oxidation: (biological) A chemical reaction that ... to life. This metabolic process provides energy fo... processes and activities. Free radical formation is ... of the oxidative process.

RDA: (Recommended Dietary Allowance): The a... vitamin or mineral that is required to meet basic n... needs, as determined by the National Research C... RDAs were first established in 1948 for a small nu... vitamins and other micronutrients. The list has sub... been expanded.