

Beta-carotene: Friend or Foe?

by Hans R. Larsen, MSc ChE

Just a short while ago beta-carotene was hailed as a powerful ally in the fight against cancer and heart disease. Today, many researchers seriously question the benefits of beta-carotene supplements. What happened? Numerous studies have shown that people who consume a diet rich in dark yellow-orange vegetables (eg. carrots) and dark green vegetables (eg. kale and broccoli) are much less likely to develop cancer and heart disease(1-8). It has also been established that people with low levels of beta-carotene in their blood have a higher incidence of heart disease and cancer, particularly lung cancer(1,3,9-14).

In 1981 it was suggested that beta-carotene is the "active component" in the protective vegetables and that supplementing with beta-carotene might prevent certain cancers(1). The idea was based on the fact that beta-carotene is an antioxidant and the most abundant carotenoid in vegetables. Antioxidants counteract the free radical-induced damage to DNA which initiates cancer(1,3,15-22). There was also considerable evidence to the effect that vitamin A prevents or retards certain cancers, so the fact that beta-carotene is readily converted to vitamin A in the liver and intestine was seen as an added bonus(1,23). More recent research suggests that beta-carotene's preventive effect is due to its antioxidant property rather than to its ability to form vitamin A(2,3,5,9,10,24).

Beta-carotene is a member of the carotenoid family and has over 500 relatives. Carotenoids are yellow-to-red pigments found in all green plant tissues and in some species of algae. So far 21 different carotenoids have been found in human blood(25). The most abundant ones are alpha-carotene, beta-carotene, lutein, lycopene, cryptoxanthin and zeaxanthin. A molecule of alpha-carotene, beta-carotene or cryptoxanthin can be split into two molecules of vitamin A in the body, but the conversion of beta-carotene is by far the most effective. The six carotenoids are all antioxidants. They are very effective in neutralizing (quenching) a highly reactive form of oxygen called singlet oxygen but also, to some extent, act to break up the chain reactions involved in lipid peroxidation (a precursor of atherosclerosis) (16,18,26- 28). Lycopene is the most abundant carotene in the human body and is by far the most effective quencher of singlet oxygen - more than twice as effective as beta-carotene(3,10,22,26,29,30).

Beta-carotene exists in several different configurations (isomers). Synthetic beta-carotene is almost 100% trans-beta-carotene; beta-carotene found in fruits and vegetables contains about 10% of cis-isomers and beta-carotene derived from algae contains about 50% of the 9-cis isomer(28,31).

The 1981 suggestion that beta-carotene might act as a cancer prevention agent led to several trials of controlled supplementation. Three of these trials focused on the prevention of lung cancer, particularly among smokers(32,33).

In 1994 Finnish researchers reported on the ATBC trial. In this study involving over 29,000 male smokers, the participants in two of four randomized groups were given 20 mg/day of beta-carotene for periods ranging from 5 to 8 years. At the end of the trial there was an 18% higher incidence of lung cancer in the supplement groups as compared to a matched placebo group(34).

At this point some researchers began to question the wisdom of beta-carotene supplementation while others dismissed the findings as a fluke. It was pointed out, quite correctly, that the actual difference in incidence rate (3.26% vs 2.76%) was quite small; it was also postulated that since many of the men had been heavy smokers for 20 years or more some of them were bound to have had the seeds of lung cancer even before the trial started(35).

In January 1996 the National Cancer Institute announced that its investigators at the Fred Hutchinson Cancer Research Center had cut short a large beta-carotene supplementation trial (CARET) involving over 18,000 smokers, former smokers and asbestos workers(36). After up to 10 years of supplementation with 30 mg/day of beta-carotene and 25,000 IU/day of vitamin

A (retinyl palmitate) and an average follow-up period of 4 years, the researchers concluded that supplementation increases lung cancer rates and mortality. The incidence of lung cancer was 28% higher, the number of deaths due to lung cancer 46% higher, and the number of deaths due to cardiovascular disease 26% higher in the supplement group than in the placebo group(37).

In May 1996 researchers from Harvard Medical School and cooperating research centers reported on a study of beta-carotene supplementation involving over 22,000 male physicians 11% of whom were smokers. Half of the physicians were given 50 mg of beta-carotene every second day while the other half were given a placebo. At the end of the 12-year study period there was no significant difference in the incidence of lung cancer, cardiovascular disease or death from all causes between the supplement and placebo groups(38).

By the Spring of 1996 the evidence could no longer be ignored. Although some supporters of supplementation continued to claim that the studies were flawed and doomed to fail, other equally responsible scientists concluded that

supplementation with large amounts of beta-carotene cannot be recommended(37,39).

So what went wrong? Is beta-carotene a friend or a foe? The answer is fairly straightforward although the explanation is anything but. Supplementing with excessive amounts of synthetic beta-carotene in isolation is of no benefit and may be harmful, especially for smokers. This conclusion in no way detracts from the epidemiologic evidence that dark green and yellow-orange vegetables protect against the development of cancer.

So why did supplementation not work? There are several possible explanations which future research will no doubt prove or disprove.

1.. All the trials used synthetic beta-carotene which is almost 100% trans-beta-carotene. Although trans-beta-carotene is well absorbed and readily converted to vitamin A, it does have a serious drawback. Intake of beta-carotene in isolation markedly lowers the concentration of lycopene in the blood; this effect is particularly significant in the case of trans-beta-carotene(28,40). Since lycopene is the most active fat-soluble antioxidant in human blood (even more active than vitamin E), a reduction of 25% or more in its concentration could have serious consequences. It is worth noting that at least one experiment has shown that supplements containing beta-carotene from natural sources do not cause a statistically significant drop in lycopene concentration(28).

2.. Some researchers are beginning to question the effectiveness of beta-carotene as an antioxidant in the human body(18,41). This scepticism applies especially to synthetic trans-beta-carotene. Recent experiments in Israel show that naturally derived beta-carotene (from *Dunaliella bardawil* algae) is four times more effective in deactivating oxidation products (conjugated dienes) than is synthetic beta-carotene(31). As a matter of fact, synthetic beta-carotene was found to be no more effective than a placebo in this particular experiment. Other experiments have shown that beta-carotene is significantly less effective than lycopene, alpha-carotene and vitamin E(10,22,30).

3.. It has never been scientifically validated that beta-carotene actually is the "active component" in cancer-preventing vegetables. Some researchers have recently suggested it is quite likely that lutein and zeaxanthin are as important or perhaps more important(8,42).

4.. The average dietary intake of beta-carotene is somewhere between 2 and 5 milligram per day, yet one of the studies added 30 mg/day of synthetic supplement; this caused the beta-carotene level in the blood to rise by a factor of 10 or more (a 1000% increase). Little is known about the effect of such abnormally high levels but they could conceivably be toxic over the long term and almost certainly will cause serious imbalances in the concentration of other important carotenes(37,39).

5.. Beta-carotene shows its greatest activity as an antioxidant at low partial pressures (tension) of oxygen such as found in blood vessels and most inner organs of the body(16,18). It is not effective at higher oxygen tensions such as would be found in the lungs. Some researchers believe that beta-carotene acts as a pro-oxidant at higher oxygen tensions(16,39). This effect is especially strong at high beta-carotene concentrations(16). Considering that beta-carotene concentrations in several of the studies were ten times the normal level it is conceivable that the pro-oxidant effect could have been magnified to such an extent that it contributed significantly to the initiation of lung cancer. No doubt other explanations will emerge for the failure of large doses of synthetic beta-carotene to prevent lung cancer

It is now clear that smokers should not supplement with beta-carotene in isolation and there seems to be no benefit of non-smokers doing so either. Both smokers and non-smokers can, however, still benefit from an increased intake of dark green and dark orange-yellow vegetables. Research shows that people with a relatively high intake of beta- carotene (6-8 mg/day) from natural sources have about half the risk of developing lung or colon cancer as do people with a low intake(5,8). Unfortunately, a recent survey carried out in the United States also shows that less than 20% of men and less than 30% of women consume the recommended five servings a day of fruits and vegetables - so there is lots of room for improvement without resorting to supplementation(43). Research into the chemopreventive properties of carotenes is continuing and new exciting developments are frequently announced. Recent studies have shown that men who consume large amounts of tomato sauce (a rich source of lycopene) have a significantly lower risk of developing prostate cancer than do men with a lower intake. Some exciting work is now also underway to evaluate lutein as a cancer-fighting agent(25,29,44). It is also possible that a beta-carotene supplement derived from natural sources and formulated so as to preserve the normal carotene ratio in the blood may be of benefit for people at high risk for cancer and cardiovascular disease. This, however, remains to be proven(44). So, until the remaining riddles in the carotene puzzle are solved, the prudent course of action is to avoid smoking and exposure to second-hand smoke and to increase the intake of protective vegetables and fruits while avoiding large intakes of any carotenoid in isolation. (See next page for references)

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