Antioxidants and Cancer

By the 1980s, numerous epidemiologic studies had shown that people with higher intakes of antioxidant nutrients had a lower risk of many different types of cancer, and beta-carotene appeared to be especially promising. For example, Dr. Peter Greenwald of the National Cancer Institute observed that "about 20 studies in various parts of the world suggest an inverse association between eating foods containing vitamin A or beta-carotene and various types of human cancer; risk is thereby reduced 30-50 percent," and by 1986, the National Cancer Institute was already sponsoring 21 clinical trials. (Greenwald, Sondik, et al., 1986) Most involved vitamin A and/or beta-carotene, but some also involved vitamin E, vitamin C, folic acid, or other nutrients. These included the ATBC trial among male smokers in Finland, the CARET trial among asbestos workers and smokers in the U.S., and the Physicians Health Study in the U.S. Although the antioxidant hypothesis was in large part based on observations of benefit from fruit and vegetable intake, none of the studies were trials relating to fruit and vegetable intake.

Many researchers have criticized some aspects of the design and the assumptions of the clinical trials on antioxidants and cancer. Trials have been undertaken with single nutrients, rather than a constellation of nutrients that occur together in foods or that have similar functions. Trials have been undertaken in populations without measuring their antioxidant status and without regard to genetic factors that may affect their risk of cancer.

Dr. Frank Meyskens and Dr. Eva Szabo observe: "It is important to recognize that micronutrients or any other dietary components do not act in isolation, but as part of a package." If the total package is required for effective function, then testing just one component is likely to be futile. They continue: "A major issue to consider is whether the scientific community is willing to take a more public health approach in addition to rethinking the reductionist medical approach in the matter of diet and cancer. In other words, do we really need to know which components of food are the active agents if changes in diet will result in reduction of cancer incidence or risk in the population at large?" (Meyskens & Szabo, 2005)

BETA-CAROTENE, VITAMIN E, AND LUNG CANCER

In the Alpha Tocopherol and Beta Carotene Study (ATBC), a large randomized controlled study in Finland, supported by the National Cancer Institute, beta-carotene and vitamin E were given to over 29,000 long-term smokers for about six years. The men had a median age of 57 at the beginning of the trial, smoked a median of 20 cigarettes per day, and had been smoking for a median of 36 years. Vitamin E supplementation (50 mg per day) increased serum levels of alpha-tocopherol by 50 percent. Beta-carotene supplementation (20 mg per day) increased serum levels of beta-carotene by 17-fold. Beta-carotene was given in a water-soluble form that had a very high bioavailability The treatments were ineffective in reducing the risk of lung cancer. In fact, there was a modest increase in lung cancer risk in smokers who took beta-carotene. (ATBC Study Group, 1994) The increase in risk was strongest in subjects who smoked at least 20 cigarettes daily and in those who drank the most alcohol. (Albanes, Heinonen, et al., 1996)

In the Carotenoid and Retinol Efficacy Trial (CARET) in the U.S., beta-carotene and high-dose vitamin A were given to a large group of smokers and asbestos workers, and were not effective in reducing the risk

of lung cancer. In fact, smokers who took beta-carotene had a somewhat increased risk of lung cancer. (Omenn, Goodman, et al., 1996)

In a third large beta-carotene trial, the Physicians' Health Trial, more than 20,000 U.S. physicians were given 50 mg of beta-carotene every other day for a period of about 13 years. No benefit was observed against cancer or heart disease in this study. Neither were there any adverse effects. (Hennekens, Buring, et al., 1996)

These three studies raise a number of questions. Shortly after publication of the studies, experts who had carefully reviewed the data were cautious about concluding that beta-carotene may actually be harmful. (Erdman, Russell, et al., 1996) Instead, they urged consideration of several points, including the following, outlined by CARIG, the Carotenoid Research Interactive Group:

- Beta-carotene is believed to be protective against the very early stages of lung cancer development. Therefore, giving beta-carotene for only a few years to high-risk lifelong smokers and asbestos workers may have been too late for it to protect against lung cancer.
- Adverse effects in the ATBC trial were primarily seen in men with the greatest intake of alcohol. It is possible that an interaction of beta-carotene, smoking, and alcohol was responsible for the apparent adverse effects.
- Fruits and vegetables contain many carotenoids and other beneficial compounds. In retrospect, it may have been unrealistic to expect a single carotenoid to achieve protective effects on its own. Research should continue on a variety of carotenoids, including beta-carotene.

In an article reflecting on the beta-carotene studies, two researchers say: "The cancer prevention community was stunned in the early 1990s" by the results of the ATBC trial and the CARET trial. It is suggested that the results "may be related to the pharmacologic doses of beta-carotene used and the resultant supra-physiologic serum concentrations of beta-carotene. This explanation is consistent with the apparent protective effect of beta-carotene on lung cancer incidence and mortality reported in observational epidemiologic studies," as well as in some clinical trials. (Duffield-Lillico & Begg, 2004)

Vitamin E was not found to have an effect in reducing the risk of lung cancer in the ATBC trial, but a 19-year follow-up analysis of the subjects in the ATBC trial recently showed that the men who had relatively higher *baseline vitamin E* levels had about a 20 percent reduced risk of cancer and heart disease during the following two decades. (Wright, Lawson, et al., 2006)

SELENIUM, VITAMIN E, AND PROSTATE CANCER

A study of selenium and skin cancer reported no effect on that primary endpoint, but researchers found a marked decrease in risk of prostate cancer in men who received selenium. (Clark, Combs, et al., 1996) The ATBC trial, which found no effect of vitamin E against lung cancer, found that the men who received vitamin E had a lower risk of prostate cancer. These two findings, together with promising epidemiologic data, formed part of the basis for launching a massive new trial on prostate cancer in 2001 (the Selenium and Vitamin E Clinical Trial, or SELECT). The SELECT trial, involving over 35,000 men who were given 200 mcg of selenium and 400 IU of vitamin E, was discontinued in 2008 because the treatments were not having a significant effect. (Lippman, Klein, et al., 2009)

In addition to considering a broader spectrum of nutrients for possible interventions, it may be important to screen study subjects according to some marker of oxidative stress or cancer risk.

Surprisingly, later followup of the participants in the SELECT trial found evidence of an increased risk of prostate cancer, after the treatment was stopped, in the men who had been given vitamin E but not in the men who had received the combination of vitamin E and selenium. (Klein, Thompson, et al., 2011) The authors indicate that a biological explanation for this observation "is not apparent from these data." They suggest that caution should be used "when recommending or studying high doses of micronutrients." They add that these essential nutrients "are part of normal physiology, and a U-shaped dose response curve may exist where either deficiency or supra-physiological doses are harmful." (Klein, Thompson, et al., 2011)

The Physicians' Health Study II (PHS II) failed to find an effect on prostate cancer or total cancer when vitamins E and C were given to more than 14,000 male physicians (average age of 64 years at the beginning of the trial) for a period of about eight years. The physicians were given 400 IU of vitamin E every other day or 500 mg of vitamin C every day, or both, or a placebo. (Gaziano, Glynn, et al., 2009)

The authors of the SELECT reflected on possible reasons why selenium appeared to be protective in an earlier trial but not in the SELECT trial. They recognized the possibility that the effect seen in an earlier trial may have been due to chance. Also, the form of selenium used in the Clark trial was not the same as the form used in the SELECT trial. They also noted that most of the benefit observed in the Clark trial was in men with low baseline selenium levels. In the SELECT trial, 78 percent of the men had higher levels at baseline and therefore may have been sufficiently replete that there was no effect of additional selenium. (Lippman, Klein, et al., 2009)

Dr. Peter Gann, in an editorial that accompanied the SELECT and PHS II reports on prostate cancer, pointed out that PSA testing became widespread at about the time the study was initiated, catching potential prostate cancer at a very early stage and leading to treatment to prevent its progression. As a result, there were relatively few cases of prostate cancer diagnosed during the trial, and most were localized and not advanced. (Gann, 2009) Dr. Gann also raises the question whether it is time to stop focusing on intervention with single agents as an approach to primary prevention.

A recent comprehensive review on selenium and human health also emphasizes the fact that the SELECT trial included almost no men with selenium levels as

low as those in the Clark trial that found a benefit from selenium supplementation on prostate cancer risk. (Rayman, 2012) The review notes that the SELECT trial does not explain the potential effects of selenium on (1) risk of advanced disease, which was present in only 1 percent of cases; (2) prostate cancer mortality, since only one SELECT participant died of the disease; (3) current smokers, who represented only 7.5 percent of the study population; or (4) as noted earlier, men with low selenium status. According to the review, "the crucial factor that needs to be emphasized is the inextricable U-shaped link with selenium status," suggesting that various health benefits could be derived from supplementation of people with low status, while people with adequate or high selenium status are unlikely to benefit and may be affected adversely. (Rayman, 2012)

ANTIOXIDANTS AND CANCER IN MEN

In the SU.VI.MAX (*Supplementation en Vitamines et Mineraux Antioxydants*) study in France, almost 8,000 women and more than 5,000 men were given an antioxidant supplement for about 7.5 years. The supplement provided 30 mg vitamin E, 120 mg vitamin C, six mg beta-carotene, 100 mcg selenium, and 20 mg zinc. Total cancer incidence and all-cause mortality were reduced in men but not in women, possibly because the men had lower antioxidant status at baseline. (Hercberg, Galan, et al., 2004)

ANTIOXIDANTS AND CANCER IN CHINA

Several intervention trials were undertaken in China, where nutritional status was relatively low. The Linxian study involved almost 30,000 adults who were given an antioxidant supplement including 50 mcg selenium, 30 mg vitamin E, and 15 mg beta-carotene, from 1985 to 1991. The treatment led to decreased risk of cancer. (Blot, Li, et al., 1993) A recent report of a 10-year follow-up of the Linxian study found that people who had received the antioxidant supplement had lower gastric cancer mortality and lower total mortality in the 10 years following discontinuation of the supplement. (Qiao, Dawsey, et al., 2009)

Where Next?

In addition to considering a broader spectrum of nutrients for possible interventions, it may be important to screen study subjects according to some marker of oxidative status or cancer risk. The study of genomics also indicates that people with different genetic profiles may vary in the way they metabolize nutrients and in their susceptibility to disease. Dr. Bruce Ames has long held that genetic variations in metabolism and in enzyme kinetics can markedly affect both normal function and susceptibility to cancer. (Ames, Elson-Schwab, et al., 2002) A recent study on breast cancer found increased risk in women who had shortened telomeres (important for stabilizing genes) and low intakes of antioxidant vitamins. (Shen, Gammon, et al., 2009) Factors such as these could potentially affect the design of new clinical trials.

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