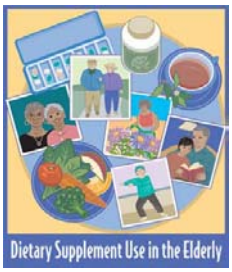

Caution in High Dose Supplement Use: A Case Study of Beta-Carotene

Robert M. Russell, M.D.

Tufts University, Boston, MA

A large body of observational epidemiologic studies has demonstrated that individuals who eat more fruits and vegetables rich in carotenoids and/or who have higher levels of serum beta-carotene have a lower risk of cancer, particularly lung cancer. However, contradictory evidence has arisen from human intervention studies using beta-carotene supplements (20-30 mg per day). An increase in risk of lung cancer among smokers who took beta-carotene supplements was reported in two trials conducted among smokers and/or asbestos-exposed workers, but not among male physicians in the United States (only 11% of whom were current smokers). We have used an animal model to study whether β-carotene supplements predispose to lung carcinogenesis and the mechanisms that are involved. When ferrets were given high dose beta-carotene supplements and exposed to cigarette smoke for 6 months, a proliferative response in lung tissue and squamous metaplasia were observed. These animals also had statistically significant lower concentrations of retinoic acid in lung tissues as well as reductions in RAR beta gene expression (a tumor suppressor gene) as compared to controls. Finally, in ferrets given high dose beta-carotene supplements and exposed to smoke, there also were elevated expressions of C-jun and C-fos genes, which are involved in cell proliferation. In a second study where ferrets were given either a physiologic dose or a pharmacologic dose of β-carotene supplementation, it was found that detrimental effects were seen only in animals given the pharmacologic doses.

Further studies have revealed an instability of the beta-carotene molecule in the lungs of cigarette smoke-exposed ferrets. Oxidized beta-carotene metabolites may play a role in the carcinogenesis by: inducing carcinogen-bioactivating enzymes, facilitating the binding of metabolites of benzo[a]pyrene to DNA, enhancing retinoic acid metabolism by P450 enzyme induction with the subsequent downregulation of RAR-beta and acting as pro-oxidants, causing damage to DNA.

Further research needs are to:

- Study the interactions of β-carotene and smoke in an animal model, where lung cancer actually develops (not just precursor lesion)
- Determine whether stabilizing the β-carotene molecule in tissue (e.g., by presense of other antioxidants) will eliminate the harmful effects of high doses
- Study the effects of lycopene in protection against lung cancer in smoke-exposed animals at both high and low dose
- Elucidate the genomics of carotenoid metabolism (e.g., can this differential absorption from individual to individual be explained by genetic differences?)
- Conduct metabolic studies on the mode of breakdown of all major dietary carotenoids (in addition to β-carotene).

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