The Interaction of Cigarette Smoking and Antioxidants. Part I: Diet and Carotenoids
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Abstract
It is logical that the requirement for antioxidant nutrients depends on a person’s exposure to endogenous and exogenous reactive oxygen species. Since cigarette smoking results in an increased cumulative exposure to reactive oxygen species from both sources, it would seem cigarette smokers would have an increased requirement for antioxidant nutrients. Logic dictates that a diet high in antioxidant-rich foods such as fruits, vegetables, and spices would be both protective and a prudent preventive strategy for smokers. This review examines available evidence of fruit and vegetable intake, and supplementation of antioxidant compounds by smokers in an attempt to make more appropriate nutritional recommendations to this population.


Introduction
It is believed the requirement for antioxidant nutrients depends on a person’s exposure to endogenous and exogenous reactive oxygen species. Since cigarette smoking results in an increased cumulative exposure to reactive oxygen species from both sources, it would seem logical a cigarette smoker would have an increased requirement for antioxidant nutrients, both dietary and supplemental. The two-fold question that must be answered is whether this logic is borne out by the research. First, does the diet of a smoker affect health outcomes, and second, does supplementing the diet of a cigarette smoker with antioxidant nutrients reduce disease risk? Answering these two threshold questions is imperative in order to give appropriate diet and supplementation guidance to individuals who smoke cigarettes.

In order to answer these questions, a review of available literature on the relationship of dietary factors and antioxidant supplements with health risks in cigarette smokers was conducted. While a variety of research has been conducted on cigarette smokers, virtually no research is available on other forms of tobacco use. Because of this limitation, for the purposes of this review, the research reviewed and conclusions drawn shall be limited exclusively to cigarette smokers.

While cigarette smoking is associated with an increased risk of many chronic diseases, from a research perspective lung cancer and cardiovascular disease have received primacy. The majority of research on the interaction of antioxidants and smoking has either directly studied incidence and mortality from these disease processes as an endpoint, or has focused on assessment of biomarkers assumed to indicate risk for these diseases.

With respect to endpoints of incidence and mortality, three long-term intervention trials have been conducted that provide data on the interaction of cigarette smoking and antioxidant supplementation. These three trials are the Alpha-Tocopherol Beta-Carotene (ATBC) Study, the Carotene and Retinol Efficacy Trial (CARET), and the Physicians’ Health Study (PHS).
Due to the volume of information, this review will be divided into two parts. Part I will focus on dietary components and beta-carotene supplementation. Part II will discuss supplementation with alpha-tocopherol, ascorbic acid, and other antioxidants.

Biomarkers and Health Risks

A variety of biomarkers have been assessed to determine, from a short-term perspective, the interactions between dietary compounds and antioxidant supplementation and health risks of cigarette smokers. Biomarkers are physiological indicators of biological processes, structure, or function. Unlike a clinical endpoint such as incidence and mortality from cardiovascular disease, a biomarker serves as a surrogate measurement because of its proven or assumed correlation with the progression or prevention of disease processes. As such, a biomarker may be a substitute for a clinical endpoint.

The advantage of using a biomarker is that a shorter duration of time is required to determine a change subsequent to an intervention. The disadvantage is that simply because a correlation between a biomarker and a clinical disease exists does not necessarily mean that altering the biomarker subsequent to an intervention will definitively alter the clinical endpoint. Currently, very few biomarkers have been unequivocally established as accurate substitutes for clinical endpoints.\(^1\) Because of this surrogate status, if research data on clinical endpoints and biomarkers is in conflict, it would seem prudent to weigh the data obtained by assessing the clinical endpoint more heavily.

The biomarkers assessed in studies of antioxidant supplementation of cigarette smokers fall into several primary categories: oxidative stress, DNA damage, and endothelial function. The rationale for the selection of these biomarkers by many researchers is they correlate with cardiovascular disease and/or cancer.

A range of biomarkers has been assessed to determine the impact of antioxidant supplementation on oxidative stress in smokers. The biomarkers assessed can be divided into \textit{in vitro} and \textit{in vivo} categories. Because of the uncertainty regarding the ultimate relationship between biomarkers of oxidative stress and clinical disease endpoints, it is not possible to definitively state which, if any, of the biomarkers is the most clinically relevant. This uncertainty is clearly reflected in the inconsistency of the biomarker selected by different researchers to determine benefit, or lack thereof, of their intervention. A brief overview of the primary biomarkers of oxidative stress encountered in research of antioxidant supplementation to cigarette smokers is provided here.

The \textit{in vitro} biomarkers of oxidative stress assess end-products created in reactions when some tissue (often red or white blood cells) is removed from the body and challenged by an oxidative stressor. Lag time and rate of LDL-cholesterol oxidation are the most common \textit{in vitro} assessments used. LDL cholesterol is isolated from a blood sample and exposed to an oxidizing agent. Lag time determines the amount of time LDL resists the specific oxidative stressor, while rate quantifies the speed of the oxidative reaction. The number of minutes LDL resists oxidation is thought to reflect the depletion of endogenous antioxidants. A longer lag time would be assumed to mean a decreased susceptibility of LDL to oxidative stress and, hence, an increased functional supply of antioxidants within the LDL. Rate of oxidation is used because it is thought a faster rate would imply the LDL is more susceptible to oxidation, while a slower rate suggests resistance and, hence, enhanced antioxidant functional capability.

The \textit{in vivo} biomarkers of oxidative stress assess end-products of reactions or biological processes that have already occurred within the body. Antibodies against oxidized LDL have been reported to be associated with cardiovascular disease.\(^2,3\) An increase in antibodies against oxidized LDL would be suggestive of increased oxidative stress exposure and also might indicate an imbalance in immune processes.
The quantity of malondialdehyde (MDA) or thiobarbituric reactive substances (TBARS) is frequently used as a biomarker of oxidative stress. MDA is a breakdown product of lipid hydroperoxides and will largely reflect metabolic by-products of oxidation of polyunsaturated fatty acids (PUFAs) containing three or more double bonds. Under circumstances of increased oxidative stress, MDA would be expected to increase.

MDA can be assessed directly, but is often determined indirectly in plasma by measuring TBARS. Measurements of TBARS are based on the reaction of MDA with thiobarbituric acid. Similar to MDA, under circumstances of increased oxidative stress to lipids, TBARS would be expected to increase. Evidence suggests plasma MDA is typically higher among smokers and TBARS correlate with the number of cigarettes smoked daily (with more cigarettes smoked resulting in higher TBARS).4

Breath pentane output (BPO) is assessed by collecting exhaled air and measuring the quantity of pentanes. Pentanes are formed in the body as a result of peroxidation of PUFAs. A portion of these pentanes is volatile and eliminated in respiration; therefore, BPO provides a functional surrogate measure of oxidative stress to lipids. BPO would be expected to increase as oxidative stress increases.

The respiratory burst reaction (RBR) is a component of the phagocytic immune response against microbial organisms. Free radical generation is a primary component of the anti-microbial mechanisms resulting from RBR. As such, a high RBR is suggestive of increased in vivo exposure to oxidative stress.

F(2)-isoprostanes are prostaglandin F isomers produced by cyclooxygenase-independent free radical peroxidation of arachidonic acid. Their quantity in plasma and urine is a functional indicator of lipid peroxidation. Under circumstances of increased oxidative stress, F(2)-isoprostanes would be expected to increase. Some researchers have suggested this is a better indicator of functional in vivo free-radical stress than in vitro assessments using lag time or oxidation rate.5

Damage to DNA is considered a precursor of cancer development. Urinary 8-hydroxydeoxyguanosine (8-OHdG) measures a repair product utilized in vivo as a response to oxidative damage to DNA. This biomarker is thought to be reflective of potentially precancerous disease processes; however, the predictive value of 8-OHdG for eventual cancer development has yet to be definitively established. Increased exposure to oxidative stress, and hence damage to DNA, would be expected to increase urinary 8-OHdG.

Micronuclei – DNA fragments in exfoliated cells – are measured to detect early-stage carcinogenesis in selected target tissues. Since an increased quantity of micronuclei in exfoliated cells reflects more damage to DNA, a higher micronuclei count would be suggestive of more DNA damage and higher risk for carcinogenesis. Similar to 8-OHdG, the predictive value of micronuclei in exfoliated cells for eventual cancer development has yet to be definitively established.

Sister chromatid exchange (SCE) in lymphocytes is used as a biomarker for in vivo cytogenic damage to DNA. While evidence suggests SCE reflects the potentially deleterious effects of cigarette smoking, the relevance of this biomarker to biological outcomes in lung tissue remains uncertain.6

Endothelial injury is a central feature of vascular disease and may act as a precursor for future atherosclerosis. Cigarette smoking has been associated with abnormal endothelial function and increased leukocyte adhesion to endothelium, both early key events in atherogenesis.7,8 Basal vasodilation and vasodilation subsequent to a challenge with nitric oxide are typically used as biomarkers of endothelial function. Adhesion of leukocytes is a less frequently encountered biomarker. A decreased vasodilatory capability in both a basal state and subsequent to challenge reflect compromised endothelial function. Similarly, an increased tendency to adhesion would indicate compromised endothelial function.
Dietary Compounds and Cigarette Smoking

Consumption of Phytonutrients: Epidemiological Evidence

Epidemiological evidence has consistently indicated that chronic cigarette smokers, as a group, consume a smaller amount of phytonutrient-rich foods. This trend has been demonstrated in smokers in the United Kingdom, Canada, the United States, and the Netherlands. The available evidence also indicates that people who would be judged as the heaviest smokers invariably consume fewer fruits and vegetables than those who smoke fewer cigarettes daily. While evidence is more limited, some epidemiological data suggest male smokers are more likely than female smokers to consume fewer fruits and vegetables. Cigarette smokers appear to make up for the caloric deficit created by consuming fewer fruits and vegetables by consuming more dietary fats, especially saturated fats.

Data extracted from the Continuing Survey of Food Intakes by Individuals (CSFII) indicates current smokers have the lowest intake of antioxidant nutrients. Fatty foods such as luncheon meats, condiments and salad dressings, and ground beef contribute more to the antioxidant intakes of current smokers than to those of non-smokers and former smokers, whereas fruits and vegetables contribute less.

Epidemiological evidence has consistently indicated a decreased risk of lung cancer among individuals consuming larger quantities of fruits and vegetables. As an example, a hospital-based case control study indicated consumption of fruits and vegetables protects cigarette smokers against lung cancer. In this study, 282 cases of lung cancer were compared with an equal number of controls. The results suggest the protective role of fruit and raw vegetable consumption might become more pronounced as intake frequency increases.

While increased fruit and vegetable intake appears to be a reasonable general recommendation to cigarette smokers, far less information exists regarding which fruits and vegetables might be most protective. From the very limited, currently available data, it appears carrots and broccoli might be two foods to advocate, and that Allium species (onions, garlic, and leeks) are relatively insignificant in altering risk status, at least with respect to lung cancer incidence.

Analysis of data from the Nurses’ Health Study suggests that alpha-carotene is the primary carotenoid associated with protection against lung cancer. Beta-carotene intake had no statistically significant association, although the trend was toward protection. Carrots contribute 3,725 units of alpha-carotene per serving and are the primary source of this carotenoid in the diet. Not surprisingly, of carotene-containing foods examined, carrot intake had the most significant interaction with lung cancer risk. Carrots were associated with a dose-dependent inverse association with lung cancer. Relative risk of lung cancer for participants who consumed five or more servings of carrots per week dropped to 0.4. Broccoli also had an inverse and dose-dependent relationship with lung cancer that reached statistical significance. Analysis of data was conducted to adjust for smoking status, indicating that consumption of these foods might be independently protective despite smoking status.

The Netherlands Cohort Study was begun in 1986 by collecting information on usual diet and important lifestyle characteristics from 120,852 men and women, ages 55-69 years. The questionnaire utilized was designed to assess onion and leek intake, as well as the use of garlic dietary supplements. Consumption of dietary garlic was not included in the questionnaire design. Data from this study indicated no apparent statistically significant protective effects of consumption of Allium-family foods with respect to lung cancer risk; however, a trend toward protection was seen in people consuming the largest amount of onions as opposed to those consuming the fewest onions. This reported data was not stratified by smoking status.
While consumption of Allium sp. in the Netherlands Cohort Study resulted in no statistically significant association with lung cancer risk, supplemental garlic was found to have an unexpected adverse association with risk. The investigators specifically examined garlic supplementation because it is among the most common self-prescribed dietary supplements in the Netherlands, especially among older people. After 3.3 years of follow-up, 550 incident lung carcinoma cases were observed. A statistically significant higher risk of lung cancer was observed for participants using garlic supplements exclusively; relative risk (RR) was 1.78 compared with participants taking no supplements. When results were stratified by smoking status, taking garlic as the only dietary supplement had a relative risk of: (1) never smoked – RR=3.27; (2) ex-smokers – RR=1.37; and (3) current smokers – RR=1.47. None of these stratified associations reached statistical significance. Among participants taking garlic plus any other dietary supplements, RR for lung cancer approximated 1.0 in current smokers and ex-smokers.17

Phytonutrient Intervention Studies: Biomarkers

No long-term intervention studies have been conducted on the effect of increased fruit and/or vegetable intake, or food supplements containing fruit and/or vegetable extracts in smokers. Several short-term interventions have been conducted examining biomarkers associated with risk.

The short-term effect of increased vegetable intake was assessed in 34 females (18 non-smokers and 16 smokers). After a depletion period of eight days consisting of avoidance of carotene-containing foods, subjects increased intake of beta-carotene- and lutein-rich (green) and lycopene-rich (red) vegetables and fruits, each for seven days. Participants were instructed to increase intake by consuming at least 200 g daily of creamed spinach and 100 g daily of mango puree during the ‘green’ week, and at least 200 g daily of tomato puree and 100 g daily of watermelon during the ‘red’ week. Total fruit and vegetable consumption was estimated at 300-400 grams daily resulting in an approximate daily intake of 25 mg of carotenoids. Supplementation of the diet with these foods resulted in significant increases in plasma and lipoprotein beta-carotene, lutein, and lycopene levels in smokers (and non-smokers) compared with baseline values. Despite this increase in plasma carotene levels, increased fruit and vegetable consumption in this trial had no observed effect on the resistance of LDL to in vitro oxidation as assessed by lag time in smokers during this short study.18

Hininger et al investigated the effects of two weeks of increased intake of fruits and vegetables on LDL oxidation. Twenty-two male and female subjects participated, with the group evenly divided between smokers and non-smokers. Fruits and vegetables were selected to provide an approximate mean daily intake of 30 mg of carotenoids (10 mg beta-carotene, 10 mg lycopene, and 10 mg lutein). The food sources of these additional carotenoids were primarily carrots, pear tomatoes, cabbage, french beans, and spinach. Baseline indices of LDL oxidation, including in vitro lag time and rate and plasma MDA, were comparable between smokers and non-smokers.19 Increased fruit and vegetable consumption resulted in a statistically significant 14-percent increase in lag time among the smokers compared to a 28-percent increase among the non-smokers. Lag rate decreased slightly in both groups but did not reach statistical significance. Taken as a whole, this is suggestive of improved resistance to oxidative processes. Plasma MDA levels decreased subsequent to increasing fruit and vegetable consumption; however, the decrease did not reach statistical significance.19

Baseline differences in plasma measurements of beta-carotene, alpha-carotene, lutein, and beta-cryptoxanthin between smokers and non-smokers reached statistical significance, with smokers having lower values of each. No statistically significant differences were observed between smokers and non-smokers for levels of lycopene, alpha- and gamma-tocopherol, and retinol at baseline. Subsequent to the two-week intervention, statistically significant increases in alphacarotene (106%), beta-carotene (41%), and lutein
(10%) were observed in smokers. In non-smokers, proportionately smaller but still statistically significant increases in alpha- and beta-carotene were observed. Despite the statistically significant increase in beta-carotene and lutein among smokers, their post-intervention plasma levels remained lower than the baseline levels among non-smokers. The substantial increase in alpha-carotene levels resulted in smokers having post-intervention plasma levels that exceeded the baseline levels in non-smokers. This increase in alpha-carotene levels is not an unexpected finding since alpha- and beta-carotene are found together in foods, and carrots were used as a component of the intervention and are a primary source of alpha-carotene in the diet.19

Smokers, somewhat surprisingly, had significantly higher baseline reduced glutathione (GSH), while the difference in oxidized glutathione (GSSG) between smokers and non-smokers did not reach statistical significance. The intervention resulted in a statistically significant decrease in GSH in smokers, with final values being comparable to those found among non-smokers. GSSG also decreased in smokers subsequent to intervention; however, the decrease did not reach statistical significance. While at first glance the drop in GSH appears to be a potentially unwanted effect, the authors suggest the initial higher GSH found among smokers might have been an adaptive response to higher oxygen radical species exposure. The decrease in GSH levels in smokers subsequent to this intervention might then be an indication of a decreased physiological need for up-regulation of GSH synthesis that occurs in smokers subsequent to increasing fruit and vegetable consumption.19 The combination of comparable post-intervention values of GSH in smokers and non-smokers and lower post-intervention GSSG in smokers than in non-smokers provides support for this adaptive GSH hypothesis.

Fifteen male smokers were given a daily beverage containing 250 mL of orange juice with a vitamin C content of 145 mg, and carrot juice with a beta-carotene content of 16 mg for three weeks. Supplementing the diet with the daily fruit/vegetable beverage raised plasma levels of ascorbic acid and beta-carotene 1.6-fold and 2.6-fold, respectively. In vivo assessment of MDA was unchanged following intervention. Rate of LDL oxidation and lag time before the onset of LDL oxidation were not affected by this beverage. Since lag rate and time are based on the formation of intermediate products of lipid peroxidation (conjugated dienes) and are thought to reflect the total amount of antioxidants functionally available in LDL, the lack of change suggests no increased ability to functionally resist lipid oxidative processes. This appears to be consistent with the lack of change of in vivo plasma MDA levels following the beverage period. The authors did observe, after the LDL was oxidized, the in vitro end product of MDA was significantly lower following supplementation with the beverage as compared with preintervention levels. It is difficult to resolve the discrepancy between this and the other observations; however, since MDA is one of only several oxidative products capable of being formed in vitro, it is possible this measurement might have underestimated the amount of stable end-products derived from lipid peroxidation subsequent to the in vitro copper challenge.20

The diet of smokers was supplemented with a proprietary aged garlic extract (AGE) in an attempt to assess the impact on plasma and urine concentrations of a specific F(2)-isoprostane – 8-iso-prostaglandin F(2 alpha) (8-iso-PGF2α). Ten smokers and 10 non-smokers were given 5 mL daily of AGE in juice for 14 days. Baseline plasma and urine concentrations of 8-iso-PGF2α were higher among smokers. Following 14 days of garlic supplementation, reductions in plasma and urine concentrations of 8-iso-PGF2α were observed in both smoking and non-smoking subjects. Average decreases were 35 percent and 48 percent in smokers, for plasma and urine 8-iso-PGF2α, respectively. For non-smokers the levels of 8-iso-PGF2α were 29 percent and 37 percent in plasma and urine, respectively. Fourteen days after cessation of dietary supplementation with AGE, plasma and urine concentrations of 8-iso-PGF2α returned to values approximately equal to baseline values.21 Since a decrease in
F(2)-isoprostanes occurs when there is a reduction in free radical peroxidation of arachidonic acid, the observations suggest an improvement in functional antioxidant capabilities.

No available evidence predicts the long-term influence of green tea consumption on clinically relevant endpoints in chronic smokers. Evidence does suggest Asian smokers who consume three or more cups per day of green tea have lower frequencies of sister-chromatid exchange than do other smokers, suggesting decreased oxidative damage to DNA and a lower risk of carcinogenesis. However, intervention with green tea as a beverage or supplement was unable to positively modify biomarkers of oxidative stress assessed in a group of smokers recruited in the Netherlands. Fifteen participants received freeze-dried green tea extracts that, when added to water, resulted in the consumption of six cups of green tea. Thirteen additional participants received a green tea polyphenol isolate in capsule form providing a daily dose of 3.6 g polyphenols. Interventions were for a four-week time period. No significant changes were observed in either lag time or oxidation rate of LDL in vitro subsequent to either intervention. A significant decrease in plasma vitamin E was observed in subjects taking the capsules containing green tea polyphenol isolate. An insignificant decrease in LDL vitamin E was also observed in these subjects. The authors suggest the polyphenol isolate might have interfered with intestinal absorption of vitamin E. Regardless of the mechanism, based on the biomarkers assessed neither form of green tea (powdered extract added to water or polyphenol isolate in capsule form) produced a positive effect in this population of smokers over a four-week time period.

No available evidence indicates whether turmeric consumption has an association with protection of risk for clinical endpoints of heart disease or cancer in cigarette smokers. Nevertheless, it has been reported that turmeric, given in doses of 1.5 g/day for 30 days, significantly reduced the urinary excretion of mutagens in smokers. Baseline urinary mutagen excretion was substantially less in six non-smokers who served as control. In the controls, addition of turmeric resulted in no further lowering of urinary mutagens.

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Summary of Phytonutrients and Smoking

Epidemiological evidence supports a general recommendation that cigarette smokers increase their overall consumption of fruits and vegetables. From the very limited currently available data, it appears carrots and broccoli might be two particular vegetables to emphasize. While increasing fruit and vegetable consumption seems prudent, long-term intervention trials to establish whether this dietary modification would positively modify disease endpoints in cigarette smokers is needed. If one fact seems clear from available data, it is that those most likely to benefit from a greater intake of fruits and vegetables are also least likely to consume them in their diets.

While a proprietary aged-garlic extract appeared to improve functional antioxidant capabilities in smokers, the epidemiological association of increased incidence of lung cancer with exclusive garlic supplementation in a cohort from the Netherlands suggests a need for more research on the long-term interactions between garlic supplementation and cigarette smoking before any definitive recommendations can be made. Short-term biomarker data suggests consuming green tea as a beverage might be an advantageous recommendation. Isolates of green tea containing simply the polyphenol component did not positively modify biomarkers of oxidative stress in the single study conducted and so should not be considered as a substitute for a smoker consuming green tea unless future research provides evidence to the contrary. Long-term intervention trials are needed to determine whether the recommendation of consuming green tea would positively modify clinical endpoints in smokers. Biomarker data supports increasing the consumption of dietary turmeric; however, long-term evidence of whether this intervention would modify clinical endpoints is currently not available.
Beta-carotene

Epidemiological studies have suggested a protective effect for dietary carotenoid intake in the prevention of lung cancer. In one epidemiological study the protective effect of carotenoids against lung cancer was particularly evident in smokers.\textsuperscript{25} Assumptions were made that beta-carotene was the primary, if not exclusive, carotenoid responsible for these observed associations. Newer research casts doubt as to whether this assumption is correct. As an example, analysis of data from the Nurses’ Health Study published in 1999 suggest that alpha-carotene is the primary carotenoid associated with lung cancer protection. Beta-carotene intake had no statistically significant association, although the trend was toward protection.\textsuperscript{16}

One study indicated that prediagnostic levels of other carotenoids besides beta-carotene appear to be inversely related to the risk of lung cancer among smokers in the United States. After adjusting for cigarette smoking, only beta-cryptoxanthin was found to have a statistically significant inverse relationship with lung cancer.\textsuperscript{26} Similar findings were reported in a cohort of Chinese men. While the carotenoids measured all had an inverse association with risk for lung cancer, only serum levels of beta-cryptoxanthin had a significant association once data was adjusted for smoking.\textsuperscript{27}

Higher blood levels of beta-carotene have consistently been found to be associated with reduced risk of lung cancer. Since smokers as a group consume fewer fruits and vegetables than nonsmokers, it was assumed that lower blood levels of beta-carotene found in this population reflected a decreased dietary intake. An assumption was then made that low levels of beta-carotene were a causative factor in lung cancer. While this assumption might be correct, an equally plausible explanation would be that, “low levels of beta-carotene may reflect the effect of disease rather than the cause.”\textsuperscript{28}

Questions of cause or effect aside, it was assumed that supplementation of a smoker’s diet with beta-carotene would reduce risk of lung cancer and possibly heart disease. However, the several large intervention trials conducted to date have failed to demonstrate reduced lung cancer incidence after prolonged high-dose beta-carotene supplementation, and have even suggested the possibility of harm. No beneficial effect on heart disease was demonstrated subsequent to beta-carotene supplementation in any of the intervention trials. The results from the intervention studies are described below. Available biomarker studies also do not support a role for beta-carotene supplementation to cigarette smokers.

Pharmacokinetics of Beta-Carotene in Smokers

Evidence indicates that supplementing the diet of cigarette smokers with beta-carotene results in substantial increases in the concentration of beta-carotene in serum and tissues. Increases in serum beta-carotene (generally on the order of 12-14 fold) are consistently observed in smokers following daily supplementation of beta-carotene in doses ranging from 15-30 mg/day.\textsuperscript{6,11,29} LDL concentrations of beta-carotene and total carotenoids have been found to increase 16.6- and 5.0-fold, respectively, subsequent to beta-carotene supplementation to smokers.\textsuperscript{30} Beta-carotene concentration in buccal mucosal cells of examined smokers was approximately seven-fold higher in supplemented subjects compared to control subjects not receiving beta-carotene.\textsuperscript{31}

Supplementing the diet of smokers with beta-carotene does not appear to interfere with the absorption of most other carotenoids. A sub-study consisting of 491 randomly selected men from the ATBC Study was undertaken to observe the long-term effects of supplemental beta-carotene (20 mg/day) on serum levels of carotenoids and to determine whether such effects might be modified by cigarette use; 254 men not receiving supplementation were used as controls. After an average of 6.7 years of supplementation, serum concentrations among the active group were 1,483-percent higher for beta-carotene, 145-percent higher for alpha-carotene, 67-percent higher for beta-cryptoxanthin, and six-percent
higher for retinol. Serum lutein levels were 11-percent lower in the supplemented group. Serum lycopene, zeaxanthin, and alpha-tocopherol did not differ between the beta-carotene and control groups. Concentrations of carotenoids were generally highest in participants who quit smoking while in the study and lowest in current smokers who smoked 20 or more cigarettes daily. This suggests that smoking, or some sequelae of smoking, had an impact on carotenoid concentrations irrespective of high-dose supplementation with beta-carotene.

Clinical Outcome Studies: Beta-carotene Intervention Trials

Alpha-Tocopherol Beta-Carotene Study (ATBC Study)

The ATBC Study was a randomized, double-blind, placebo-controlled primary-prevention trial designed to determine whether daily supplementation with alpha-tocopherol, beta-carotene, or both would reduce the incidence of cancer, especially lung cancer, among cigarette smokers. The study included 29,133 male smokers, ages 50 to 69 years at entry; average age 57.2 years. All subjects smoked five or more cigarettes daily with an average daily cigarette intake of 20.4. Participants had an average smoking history of 35.9 years. Subjects were recruited from southwestern Finland. Participants were randomly assigned to one of four intervention groups: (1) alpha-tocopherol (50 mg/d as a 50-percent powder of synthetic dl-alpha-tocopherol); (2) beta-carotene (20 mg/d as 10-percent water-soluble beadlets of synthetic beta-carotene); (3) alpha-tocopherol (50 mg/d) and beta-carotene (20 mg/d); or (4) placebo. Follow-up occurred over a 5-8 year time interval.

With respect to beta-carotene supplementation, the results of the ATBC Study were not promising, at least for male Finnish smokers. Overall mortality was eight-percent higher among subjects receiving beta-carotene compared to subjects not receiving beta-carotene. This increased mortality was primarily accounted for by increased deaths from lung cancer and ischemic heart disease (IHD) (Figure 1).

During the 5-8 year follow-up period, 876 new cases of lung cancer were diagnosed. The incidence of lung cancer was 18-percent higher among subjects receiving beta-carotene compared to subjects not receiving beta-carotene. This increased mortality was primarily accounted for by increased deaths from lung cancer and ischemic heart disease (IHD) (Figure 1).
follow-up and increased progressively at each subsequent follow-up evaluation. 33

In an effort to determine whether any subgroups were at higher or lower risk, baseline lifestyle factors, including alcohol consumption and number of cigarettes smoked daily, were compared. The incidence of lung cancer was higher among subjects smoking at least 20 cigarettes daily (RR=1.25) compared with those smoking 5-19 cigarettes daily (RR=0.97). The incidence of lung cancer was also higher (RR=1.35) among subjects consuming more than 11 g ethanol daily (equivalent to just under one drink per day) compared with those with a lower daily intake (RR = 1.03). 34 These observations suggest the number of cigarettes smoked and the amount of alcohol consumed daily might interact with beta-carotene in some manner to influence the risk of lung cancer among smokers.

In the group as a whole, beta-carotene had no statistically significant effect on other types of cancer. There was no statistically significant evidence of an interaction between beta-carotene and alpha-tocopherol with respect to protection against lung cancer occurrence. The incidence rate of lung cancer per 10,000 person-years for those taking beta-carotene alone was 57.2; those taking beta-carotene and alpha-tocopherol was 55.3; while those taking placebo or alpha-tocopherol alone had incidence rates of 47.7 and 47.3, respectively. 33 This seems to suggest, at least with respect to this population, a lack of antioxidant synergism with the combination of beta-carotene and alpha-tocopherol.

No effect, either protective or harmful, of beta-carotene supplementation was observed for a subset of 409 subjects with respect to the development of oral mucosal lesions. 35 The lack of protective effect was observed despite the fact that beta-carotene concentration in buccal mucosal cells was approximately sevenfold higher in supplemented subjects compared to control subjects. 31 There was no statistically significant increase in incidence of and mortality from IHD among participants receiving beta-carotene. 33 Analyzing data for stroke did result in a statistically significant relationship between beta-carotene supplementation and risk of intracerebral hemorrhage. Using only participants who were stroke-free at baseline (28,519 subjects) as a cohort and an endpoint of a first stroke incident during the intervention period, a 62-percent increased risk of intracerebral hemorrhage among subjects receiving beta-carotene supplementation was observed; however, overall effects on incidence and mortality of total strokes did not reach statistical significance. 36 Table 1 shows stroke incidence in the ATBC Study subgroup of participants who were stroke-free at baseline.

The influence of beta-carotene supplementation on the incidence of self-reported cold episodes was observed in a subset of 21,796 male smokers over a four-year follow-up period. No association with beta-carotene supplementation and incidence rate of self-reported cold episodes was observed. 37

**Carotene and Retinol Efficacy Trial (CARET)**

CARET was a randomized, multi-center, placebo-controlled trial designed to determine the effects of beta-carotene and retinol in subjects at high risk for lung cancer because of a history of cigarette smoking and/or an occupational history of asbestos exposure. Enrollment began in 1985 and initially was termed a pilot study. It consisted of 816 males with an occupational exposure to asbestos (with no requirement for smoking status) and 1,029 persons with extensive histories of cigarette smoking. During this pilot study participants were divided into four groups: (1) beta-carotene (15 mg/d for those occupationally exposed to asbestos and 30 mg/d for those with a history of cigarette smoking); (2) retinol (25,000 IU/d); (3) a combination of both beta-carotene and retinol; or (4) placebo. Enrollment was expanded in 1988 and 1991, resulting in a total of 4,060 workers exposed to asbestos (with no requirement for smoking status) and 1,029 persons with extensive histories of cigarette smoking. During this pilot study participants were divided into four groups: (1) beta-carotene (15 mg/d for those occupationally exposed to asbestos and 30 mg/d for those with a history of cigarette smoking); (2) retinol (25,000 IU/d); (3) a combination of both beta-carotene and retinol; or (4) placebo. Enrollment was expanded in 1988 and 1991, resulting in a total of 4,060 workers exposed to asbestos (with new participants required to be either current or former smokers) and 14,254 male and female heavy smokers (defined as current or past smokers with at least a 20 pack-year history). With the expansion of enrollment in 1988, the intervention was
**Table 1. Stroke Incidence and Mortality in an ATBC Study Subgroup**

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consolidated so all participants in the active intervention group received either retinol (25,000 IU/day) plus beta-carotene (30 mg/day) or placebo.

The age range of participants was 45-74 years at enrollment. Since most of the individuals exposed to asbestos had either previously smoked or were current smokers, of the total 18,314 male and female subjects enrolled, approximately 60 percent were current smokers and 39 percent were ex-smokers upon randomization to an intervention group. Smokers were encouraged to quit smoking and smoking cessation assistance was provided to those who desired. Approximately five percent of smokers ceased smoking each year. Subjects were recruited from multiple study centers primarily located in the Pacific Northwest of the United States. The trial was intended to last until late 1997, which would have allowed for a six-year follow-up for all participants; however, CARET was stopped in December 1995 because available endpoint evidence indicated no benefit and a possibility of unwanted effects. At termination the mean follow-up was 4.0 years.38,39

CARET was terminated 21 months early because interim evaluation of data indicated that, should the trial continue for its scheduled duration, it was unlikely the intervention would produce a beneficial effect. The interim data also suggested a possibility the group receiving the active intervention of a combination of beta-carotene and retinol might be at increased risk of lung cancer.38,39

Lung cancer incidence was considered the primary endpoint of CARET.38 As of the December 1995 termination date, 388 participants were reported to have developed lung cancer, with mortality of 254.38 In the active intervention group as a whole there was a 23-percent greater incidence of lung cancer and 17-percent more deaths from all causes.39

After assessing data at 18 months, the first observation of an increased incidence of lung cancer among persons in the active treatment group was noted. This trend persisted throughout the duration of follow-up. Among participants as a whole, this resulted in a statistically significant relative risk of lung cancer incidence of 1.28 for participants receiving the active intervention. For those in the heavy smoking group, relative risk with the active intervention was 1.42 (95% confidence interval, 1.07-1.87). Among subjects who had ceased smoking two or more years prior to entry into the trial, a trend toward a protective effect of the active intervention was observed, with a relative risk of 0.80 (95% confidence interval, 0.48-1.31).38

Among all subjects receiving active treatment the relative risk of death from all causes was 1.17. For heavy smokers as a subgroup the relative risk was 1.13. While these observations were statistically significant, there was no statistically significant difference in mortality between heavy smokers who were smoking as opposed to those who had ceased smoking at the time of randomization. The excess mortality was largely accounted for in the groups as a whole by increased mortality from lung cancer (1.46, 95% confidence interval, 1.07-2.00) and cardiovascular disease (1.26, 95% confidence interval, 0.99-1.61). Mortality information for lung cancer and cardiovascular disease was not stratified by smoking status. Similar to the incidence of lung cancer, mortality differences between the active and placebo groups did not appear initially; however, by 24 months they were apparent and remained so until the trial was terminated.38

The safety and endpoints monitoring and steering committees, after the second interim analysis, ended the trial because of the “extremely limited prospect of a favorable overall effect, as well as the possibility of true adverse effects.”38 Since subjects received either the combination of beta-carotene and retinol or placebo, it is not possible to draw definitive conclusions about the impact of beta-carotene supplementation in isolation.

Physicians Health Study (PHS)

PHS was a long-term randomized, double-blind, placebo-controlled intervention trial designed to monitor the end points of cancer and cardiovascular incidence and mortality. PHS began in 1982 and included 22,071 male physicians with an age range of 40-84 years. At the start of the trial 11 percent of enrolled physicians were active smokers and 39 percent were former smokers. The
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interventions consisted of: (1) 50 mg beta-carotene every other day, alternating with placebo; (2) 325 mg aspirin every other day, alternating with placebo; (3) 50 mg beta-carotene every other day, alternating with 325 mg aspirin; or (4) placebo given every day. The aspirin component of the trial was ended in 1988 when interim analysis of the data indicated a statistically significant benefit of the intervention on risk for a first myocardial infarction. After this, physicians were allowed to take aspirin in lieu of the placebo in the two groups previously not receiving aspirin. The result was that for the trial period between termination of the aspirin component in 1988 and termination of the beta-carotene component in December 1995 the intervention for the majority of the 22,071 participants consisted of: (1) on alternate days participants received placebo and 325 mg aspirin; or (2) on alternate days participants received 50 mg beta-carotene and 325 mg aspirin. The intervention period ended as scheduled on December 31, 1995. At completion, all 11,036 participants had been receiving beta-carotene and 11,035 had been receiving placebo for at least 11 years (the last seven years of which the majority had been receiving aspirin independently of beta-carotene status).

Incidence of and mortality from cancer showed no statistically significant interactions with beta-carotene supplementation among participants in PHS. There was also no statistically significant association, either protective or harmful, of beta-carotene supplementation on incidence of and mortality from lung cancer, with 63 deaths from lung cancer occurring in participants receiving beta-carotene and 62 deaths in those receiving placebo. When results were stratified according to smoking status at entry, no statistically significant associations were found among participants.

When the end-point of cardiovascular disease was assessed, results mirrored those found with cancer. When analyzing the group as a whole or stratified by smoking status, no statistically significant trends toward either protection or harm of beta-carotene supplementation were found.

Biomarker Studies: Beta-carotene

Reviewing only biomarker studies conducted on active smokers, the available evidence is not supportive of a substantial role for beta-carotene in positively modifying any of the observed biomarkers. The effects of beta-carotene on biomarkers of oxidative stress and DNA damage were inconsistent. This inconsistency is not surprising when it is considered that beta-carotene’s antioxidant activity varies depending upon experimental circumstances.

Beta-carotene is generally referred to as an antioxidant nutrient, although it is not the case in all situations. Quoting from Pryor et al, “[beta carotene] ... is neither a generalized reducing agent nor a universal antioxidant. Although beta-carotene, as well as other carotenoids, can demonstrate antioxidant properties in some systems, the potency of beta-carotene appears to vary from system to system for reasons that are very poorly understood ... for example, in a variety of in vitro model systems, the antioxidant properties of beta-carotene vary from virtually non-existent to quite modest to very strong. It is more difficult to obtain in vivo evidence, but in humans beta-carotene sometimes does and sometimes does not demonstrate antioxidant properties.”

For an in-depth treatment of the antioxidant/pro-oxidant effects of beta-carotene, the reader is referred to reviews by Edge et al, Palozza and Krinsky, and Palozza.

In vitro and in vivo studies might shed a small degree of light on the present conundrum regarding the antioxidant status of beta-carotene in smokers. It appears beta-carotene may act as an anticarcinogen, but its oxidized products can facilitate carcinogenesis. Beta-carotene appears to act either as an antioxidant or pro-oxidant in vivo depending on circumstances such as smoking. If this hypothesis is true, the carcinogenic response to high-dose beta-carotene supplementation reported in the human intervention trials in smokers might be related to the instability of the beta-carotene molecule in the free radical-rich environment in the lungs of cigarette smokers. More research is required to determine if this is, in fact, the case.
Beta-carotene has been investigated for its antioxidant activities in smokers by assessing biomarkers of oxidative stress. Nothing in the available results definitively explains the increase in clinical endpoint incidence and mortality found in the intervention trials.

Supplementation of 9 mg beta-carotene daily for four weeks did not result in a statistically significant decrease in elevated MDA levels found in subjects smoking 20 or more cigarettes daily.47 Supplementation of 40 mg beta-carotene or placebo daily to 23 non-smokers and 46 cigarette smokers (at least 15 cigarettes daily) for two weeks, followed by an additional 12 weeks of supplementation with 20 mg, resulted in no clinically relevant change in the biomarkers of oxidative stress assessed. Beta-carotene resulted in a slight prolongation of in vitro lag time from 106 to 112 minutes and no significant change in propagation rate.30 This minor extension of lag time is likely to be clinically irrelevant when one considers the lag time found in non-smokers is substantially longer. Supplementation with 20 mg beta-carotene daily for four weeks reduced BPO in smokers, suggesting an in vivo antioxidant effect.48

Daily supplementation with 9 mg beta-carotene for four weeks to participants smoking 20 or more cigarettes per day resulted in a decrease of 19.8 percent in white blood cell (WBC) levels of 8-OHdG, suggesting a reduction of oxidative damage to DNA.49 Since urinary 8-OHdG is considered a biomarker of potential oxidative stress, it is not clear why the authors chose to assess WBC levels or what clinical relevance this might have. In the only study available assessing urinary 8-OHdG as a biomarker, 20 mg beta-carotene provided daily for 14 weeks resulted in no significant change in urinary 8-OHdG in smokers compared with placebo.50

The effect of 14 weeks of beta-carotene supplementation on the frequency of SCE in lymphocytes in 143 heavy smokers was investigated. Participants were given capsules containing 10 mg beta-carotene or placebo twice daily for two weeks followed by one capsule daily for an additional 12 weeks. Almost identical decreases in SCE were found among both beta-carotene and placebo groups during the study.6 Supplementation of a higher dose (40 mg/d) of beta-carotene for six weeks to cigarette smokers was also unable to impact SCE.51 The results do not support a protective effect of beta-carotene on this biomarker of DNA damage.

In a double-blind trial, Van Poppel et al investigated the effect of 14 weeks of beta-carotene supplementation on the frequency of micronuclei in sputum in 114 heavy smokers. Participants took two capsules of beta-carotene (20 mg/day) or placebo for two weeks and then one capsule daily for an additional 12 weeks. Participants smoked 15 or more cigarettes daily for a minimum of two years. At baseline a substantial interindividual variation in micronuclei counts existed, with some subjects having values close to zero micronuclei per 3,000 cells and others having values in excess of 14 micronuclei per 3,000 cells examined. Subjects receiving beta-carotene supplementation had an average decrease of 47 percent in micronuclei counts, while subjects in the placebo group had an average decrease of 16 percent. After adjusting for differences in initial micronuclei levels between groups, supplementation of beta-carotene resulted in micronuclei counts 27-percent lower than placebo.52

Because of the substantial individual variability and the variable response to supplementation with beta-carotene, it is impossible to use these results to support supplementation of beta-carotene to smokers as a group, although individual smokers in this study did benefit with respect to this biomarker of carcinogenesis.

**Beta Carotene and Smoking: Discussion**

In the ATBC Study, CARET, and PHS, supplementing the diet of smokers with beta-carotene (either alone or in combination with alphatocopherol, retinol, or aspirin, respectively) demonstrated no benefit with respect to clinical endpoints of incidence of and mortality from cancer and cardiovascular disease. In the ATBC Study and CARET (but not in PHS) statistically significant associations with supplementation of beta-carotene and an increased relative risk for certain
clinical endpoints were actually observed, suggesting the possibility that supplementation of the diet of active smokers with beta-carotene might in fact be detrimental.

In both ATBC and CARET, the increased risk subsequent to supplementation was not apparent for 18-24 months. After this point, the increased risk became and remained apparent (and actually continued to increase slightly with longer duration of supplementation) until the trials were terminated. This does not seem to be consistent with arguments that suggest beta-carotene would be more beneficial if given earlier to smokers (in a precancerous stage), or the supplementation period was not long enough. In fact, the opposite appears as likely, if not more likely, to be the case.

Only one study has looked at subsets of smokers to identify whether other factors might increase or decrease risk of unwanted clinical endpoints subsequent to beta-carotene supplementation. By stratifying participants of the ATBC Study into subsets based on the number of cigarettes smoked daily and daily alcohol intake, some trends became apparent. The incidence of lung cancer was higher among subjects smoking at least 20 cigarettes daily compared with those who smoked 5-19 cigarettes daily (who had no increased risk). The incidence of lung cancer was also higher among subjects consuming just under one drink per day compared with those with a lower daily intake (who had no increased risk).35

If these observations are accurate, it indicates beta-carotene might be most, if not exclusively, detrimental to heavy smokers and/or frequent consumers of alcohol. These observations also suggest the potential need for increased stratification of smoking populations in order to provide more accurate and useful nutritional advice.

Mounting evidence suggests the whole family of carotenoids might be more biologically important than beta-carotene alone in reducing lung cancer risk. The limited available data does not indicate that supplementing beta-carotene in isolation to smokers interferes with absorption of any carotene, with the possible exception of lutein. In fact, supplementation with beta-carotene resulted in higher serum concentrations of not only beta-carotene but also alpha-carotene and beta-cryptoxanthin.

There is currently no consensus whether beta-carotene would act as an antioxidant, pro-oxidant, or neither in smokers if given for prolonged periods of time (as was the case in the intervention trials). The available data on short-term biomarkers of oxidative stress appears to indicate beta-carotene has no clinically significant impact on in vitro lag time or rate, in vivo MDA levels, or urinary 8-OHdG, but may provide possible benefit on BPO. Taken as a whole, the results of the biomarker assessments on beta-carotene supplementation to smokers are not impressive and do not warrant an expectation of long-term clinically relevant reductions in the oxidative stress induced by cigarette smoking.

The lack of effect of supplementing the diet of smokers with beta-carotene on SCE and the variable response elicited in exfoliated micronuclei (many smokers experiencing a decrease but some experiencing a paradoxical increase) would seem to weaken any claim in favor of beta-carotene as a predictable means of reducing DNA damage in smokers.

Consistent observation of inverse relationships between beta-carotene levels and risk for chronic disease, such as heart disease and lung cancer, can readily lead to an explanation of decreased dietary intake. While this is one explanation, it is not the only explanation. In fact, some evidence suggests smokers have lower levels of serum beta-carotene than non-smokers independent of intake.53

A possible explanation for the observed low beta-carotene levels in smokers could also be that serum beta-carotene levels reflect not only dietary intake but also are responsive to other non-dietary factors and/or physiological processes. In other words, beta-carotene levels in the blood might vary independently of dietary intake and be a biomarker for other forces. If this were the case, increased intake of beta-carotene would not be expected to protect against disease since it was a biomarker of some other process and not indicative of low dietary intake. As an example, use of oral contraceptives has been shown to have a strong negative relationship with serum beta-carotene levels independent of dietary intake.54
Starting from a hypothesis that beta-carotene levels might be inversely associated with inflammation, and building on evidence that smokers have higher levels of C-reactive protein, Ras investigated the relationship between this biomarker of systemic inflammation and serum beta-carotene levels. Using data from participants in the Third National Health and Nutritional Examination Survey (NHANES III), an inverse relationship between serum beta-carotene and C-reactive protein was observed for smokers and non-smokers. After adjustment for carotene intake and other potentially confounding factors, a statistically significant relationship between C-reactive protein and serum beta-carotene levels was observed in smokers, ex-smokers, and non-smokers.55

If this relationship between beta-carotene levels and markers of systemic inflammation is indeed valid in smokers (and non-smokers) it would point to a tremendous limitation in using serum levels of beta-carotene and possibly other nutrients as reflections of dietary intake. It would also partly explain why, despite the low serum beta-carotene levels routinely observed among cigarette smokers, supplementation with beta-carotene has been ineffective as an intervention. The low observed serum beta-carotene might not indicate an insufficient intake of beta-carotene in smokers. Instead it might simply be an indication the person is faced with greater systemic inflammatory processes. In the words of several researchers, ... at least to some extent, reductions in beta-carotene appear to act as a biomarker for smoking.”56

Conclusion
The ATBC Study raised the possibility that supplementation of vitamins to smokers might not only fail to provide protective benefits, but might actually have deleterious effects. CARET provides additional support for this possibility.

It is currently not possible to definitively explain the apparent increased risk of lung cancer and IHD incidence and overall mortality resulting from beta-carotene supplementation, whether alone or in combination with either alphatocopherol or retinol in the intervention studies in smokers. What does seem to be true is: (1) as a group, smokers respond differently to beta-carotene supplementation than do non-smokers; (2) the combination of beta-carotene with other nutrients to date has not produced favorable outcomes in smokers; (3) available biomarker data does not support a definitive positive role for beta-carotene modifying disease risk; and (4) it cannot be ascertained whether low serum levels of beta-carotene reflect a cause or effect in smokers. Taking this information as a whole, it seems unjustified to advocate supplementing a smoker’s diet with beta-carotene. In fact, one might be more justified advocating against supplementation of this nutrient to smokers based on available evidence.

Epidemiological evidence supports a general recommendation that cigarette smokers should increase their overall consumption of fruits and vegetables. It is important to note that no long-term intervention data is available to determine whether actually increasing fruit and vegetable intake will result in a decrease in incidence and mortality from heart disease and/or cancer in smokers. While increased intake of fruits and vegetables appears to be a reasonable general recommendation to cigarette smokers, far less information exists on which specific fruits and vegetables might be most advantageous. From the very limited currently available data, it appears carrots and broccoli would be two such foods to advocate.

The cancer-protective effect of fruits and vegetables in smokers seems to rely not on the effect of any single compound but rather on eating the food itself. As such, eating carrots appears to be a prudent recommendation; supplementing beta-carotene in isolation does not. Eating garlic appears to be benign; supplementing garlic has an epidemiological association with increased lung cancer. A history of drinking green tea results in fewer SCE in smokers, yet taking an isolate of green tea polyphenols may negatively impact vitamin E status and was unable to positively modify biomarkers of oxidative stress. Until more evidence is available, smokers should be approached as a unique group, a group in which paradoxical results of supplementation are possible.
References


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**UA Program in Integrative Medicine Receives NIH Grant to Establish Research Training Program in Alternative and Complementary Medicine**

From: George Humphrey, (520) 626-7301  
Aug. 26, 2002

The *Program in Integrative Medicine* at the University of Arizona Health Sciences Center has received a major grant from the National Center for Complementary and Alternative Medicine (NCCAM) to establish the *Arizona Complementary & Alternative Medicine Research Training Program (ACAMRTP)*.

Part of the National Institutes of Health, NCCAM will provide $1.3 million over five years to the UA to establish ACAMRTP, an interdisciplinary clinical research training program to prepare outstanding research scientists for academic careers in integrative medicine.

Principal investigator Iris Bell, MD, PhD, Director of Research for the UA Program in Integrative Medicine and UA professor of psychiatry, psychology and public health, said the new research training program will investigate the processes and outcomes of integrative clinical care, methodological challenges in integrative medicine and healing mechanisms. Faculty will represent diverse disciplines, including medicine, nursing, pharmacology, complementary and alternative medicine, psychology, anthropology, epidemiology, nutrition, and public health. Training will focus in qualitative methods, outcome tool development and validation, observational designs, health care economic analysis, health services research, randomized controlled trials and other efforts, according to grant information.

The program will enroll two predoctoral, two postdoctoral and two short-term clinical undergraduate trainees in 2002-2003. For more information about this program, please call (520) 626-3512; email resinfo@ahsc.arizona.edu, or see website: [http://integrativemedicine.arizona.edu/research/rt32.html](http://integrativemedicine.arizona.edu/research/rt32.html)