Introduction

The interplay between nutrition and chronic disease is one which has been the focus of a growing body of medical literature. Botanical compounds, in particular, have been recognized for their potential to prevent long-term disease and thus remain active areas of pharmaceutical investigation utilizing modern computational, bioinformatics, and high-throughput screening systems[1]. In this light, the present review shall examine the relationship between carotenoid intake and the incidence of lung cancer in adults.

Lung cancer remains the leading cause of cancer death in the United States, comprising nearly 30% of all cancer-related mortality[2]. Despite persistent investigation into various therapeutic modalities, the five-year survival rate for lung cancer patients remains at 15% and has witnessed little progress over the past 30 years[3]. The aggressive nature of this tumor and its propensity for hematogenous spread are regarded as major contributory factors to its poor prognosis[4].

Efforts aimed at reducing lung cancer incidence have focused upon smoking cessation, reduction in occupational insults such as asbestos, and various forms of nutritional supplementation. With regards to the latter, carotenoids have been examined for broad-spectrum anti-neoplastic activity against a variety of tumors, including lung cancer[5]. Carotenoids are colorful, fat-soluble pigments accounting for the red, orange, and yellow color of multiple fruits and vegetables. All photosynthetic organisms contain carotenoids since these compounds serve as accessory photosynthetic pigments and also exert a photoprotective effect via their anti-oxidant activity. While over 600 naturally occurring carotenoids have been identified[6], only the following six are of significance in the human body: alpha-carotene, beta-carotene, lycopene, lutein, zeaxanthin, and cryptoxanthin. Additionally, over fifty natural carotenoids, including alpha- and beta-carotene, have the potential for conversion into retinal and subsequently retinol (vitamin A) in the intestinal mucosa, hence these compounds are referred to as provitamin A carotenoids[6]. Vitamin A, in turn, is essential for a variety of physiologic functions, including vision, epithelial regulation, immunomodulation, and embryonic development[7]. The precise function of non-provitamin A carotenoids remains obscure, though they may exert protective effects against stroke, aging, macular degeneration, ischemic heart disease, and cancer[8].

Observational Evidence Relating Carotenoid Intake to Reduced Lung Cancer Incidence

With this, one may now begin to analyze the current body of literature examining the relationship between carotenoid intake and lung cancer incidence. As noted by Ziegler et al. (1996), the uniformity of results from observational studies is quite salient, with eighteen of twenty retrospective studies and eight of eight prospective studies yielding an association between increased carotenoid intake and reduced lung cancer incidence[9].

However, the true relationship between lung cancer and carotenoid consumption is much more complex, largely due to several contradictory results in the current literature. For example, Alavanja et al. (1993)[10] found beta-carotene and total vegetable intake to be non-protective against lung cancer in non-smoking females, whereas another study reported a significant reduction in lung cancer both in non-smoking men and women with increased beta-carotene and vegetable intake[11]. One possible confounding factor accounting for such discrepancies may have been the manner in which the food was prepared. For example, cooking fruits/vegetables has been shown to damage xanthophyllic carotenoids yet simultaneously increase the bioavailability

of alpha- and beta-carotene. As noted by Mayne (1996), it is therefore essential that future basic science and epidemiologic investigations attempt to define the complex effects of food preparation on systemic carotenoid availability and subsequent cancer reduction[8].

Given the mounting observational evidence suggesting an inverse relationship between carotenoid intake and lung cancer incidence, multiple beta-carotene intervention trials were initiated using lung cancer development as a primary endpoint. Two such trials, the Alpha–Tocopherol Beta–Carotene (ATBC) trial and the Carotene and Retinol Efficacy Trial (CARET), have been completed and shall be reviewed at present.

Unanticipated Results of the CARET and ATBC Trials

As noted by Peto et al. (1981), the risk of developing several human cancers is inversely related to both blood retinol levels and dietary beta-carotene intake[12]. Although this is suggestive of a cancer-protective role for these agents, it is far from a causal relationship given the myriad of external factors which may effect systemic concentrations of these compounds. Hence, properly controlled intervention trials may be the best way to evaluate the relationship between carotenoid intake and carcinogenesis. To this end, the ATBC trial was a randomized, double-blind, placebo-controlled primary-prevention trial in which the effects of daily supplementation with beta-carotene, vitamin E (alpha-tocopherol), or both on lung cancer incidence were examined[13]. Over 29,000 male smokers from southwestern Finland between the ages of fifty and sixty-nine were enrolled in the study and assigned to one of four treatment regimens: 1) beta-carotene (20 mg/day). 2) alpha–tocopherol (50 mg/day). 3) both beta–carotene (20 mg/day) and alpha–tocopherol (50 mg/day). 4) placebo. Follow-up was continued for up to eight years, during which time the authors observed 876 new cases of lung cancer. No protective effect for alpha-tocopherol was noted. Surprisingly, a significantly higher incidence of lung cancer was observed among men receiving beta–carotene supplementation. Additionally, no evidence of interaction between alpha–tocopherol and beta–carotene in relation to lung cancer incidence was observed[13]. As a result, the authors concluded that there was no significant attenuation of lung cancer among male smokers after several years of alpha–tocopherol and beta–carotene supplementation. They also noted that their unexpected results raised concern over the potentially harmful effects of such compounds.

Indeed, the results of the ATBC trial were unanticipated in light of the earlier mentioned observational studies which were extraordinarily consistent in demonstrating cancer-protective effects associated with carotenoid intake. Although one may be inclined to attribute this discrepancy to some fault of the ATBC study design[14], the fact that the CARET trial produced similar results diminishes the prudence of this argument.

The CARET trial was also a multicenter, randomized, double-blind, placebo-controlled primary prevention trial[15]. The study population consisted of over 18,000 smokers, former-smokers, and workers with significant occupational exposures to asbestos. Participants were randomly assigned in a 1:1 ratio to receive one of two possible treatments: 1) a combination of 15 mg beta–carotene/day and 25,000 IU retinol/day (active-treatment). 2) placebo. During follow-up (mean follow-up = 4 years), the authors observed 388 new cases of lung cancer with the active treatment group having a relative risk of 1.28 for developing lung cancer in comparison to the placebo group. The active-treatment group also displayed relative risks of death from any cause and death from cardiovascular disease of 1.17 and 1.26, respectively. Given these unexpected results, the steering committee decided on January 11, 1996 to terminate

the experiment nearly two years earlier than anticipated, although follow-up was to continue for an additional five years. Indeed, the authors themselves noted their results to be troubling, particularly given that the active-treatment group displayed a 28% higher incidence of lung cancer in comparison to those receiving placebo.

Hence, the combined results of the ATBC and CARET trials suggest that beta–carotene supplementation is not protective and indeed may be harmful to those individuals seeking to reduce their probability of developing lung cancer via nutritional supplementation. Given that public health recommendations often rest upon the results of such trials, one must attempt to postulate mechanisms behind these data in order to ensure optimal supplementation with carotenoid micronutrients. This shall be the subject of the next portion of this review.

Hypotheses Regarding Discrepancies Between Observational Data and the CARET/ATBC Trials

In short, there is no simple answer to this dilemma, although several hypotheses have been put forth. The authors of the ATBC trial noted that their intervention period may have been too short to inhibit oncogenic processes resulting from decades of cigarette smoking and other carcinogenic insults[13]. They also concede that beta–carotene may not be the active anti-cancer agent in fruits and vegetables but rather may simply serve as a non-specific marker for anti-cancerous dietary habits.

Interestingly, the authors of the CARET trial postulated that beta–carotene levels above an unidentified threshold may potentially be toxic or alter the bioavailability of other essential micronutrients[15]. This may certainly be possible, particularly in light of the work of Krinsky (1993) and Burton and Ingold (1984) suggesting that beta–carotene may actually exert pro-oxidant activity under non-physiologic conditions such as those induced during artificial supplementation[16,17]. The CARET authors also noted that the widespread conclusion of carotenoids having anti-cancerous effects drawn from observational studies may not be accurate given that such studies largely ignore or poorly adjust for critical variables such as physical activity, red meat consumption, and other patterns of dietary intake[15].

Another intriguing critique of the CARET trial stems from its statistical utilization of interim analysis. As noted by Mayne, although Omenn et al. (1996) provided a p-value of 0.032 for lung cancer development in subjects receiving active treatment, one cannot accurately accept this as statistically significant evidence of harm[8]. Specifically, studies employing interim analyses must have more rigorous significance levels for each subsequent round of data examination. That is, if a given data set is analyzed enough times during a large trial, a p-value of <0.05 would be expected to emerge regardless of whether or not a true difference between outcomes existed[18].

Logically, additional baseline characteristics such as smoking intensity, nutritional status, mental well-being, alcohol consumption, and the presence of co-morbidities may have influenced the outcomes of both the CARET and ATBC trials. Yet such factors would only explain a lack of lung cancer protection with carotenoid intake. This is quite distinct from an increased risk of cancer with carotenoid ingestion, which is much more arduous to account for. Aside from the pro-oxidant hypothesis of beta–carotene at non-physiologic conditions mentioned earlier, some have postulated that high doses of beta–carotene may actually impair intestinal absorption of other vital nutrients and anti-oxidants, thereby imposing a carcinogenic risk[19]. Others have hypothesized that supplemental beta–carotene may effect the bioavailability of other

carotenoids, including alpha−carotene, lutein, lycopene, and zeaxanthin[20-22]. For the most part, these hypotheses have received some degree of support in the laboratory but are far from substantiated.

Hence, the assumption that random chance accounts for the similar conclusions reached by the CARET and ATBC trials in the setting of double-blind, randomized, placebo-controlled environments appears questionable at best and misleading at worst. Despite the large body of observational epidemiologic data identifying beta−carotene as a protective agent against lung cancer, the results of these controlled intervention trials must not be overlooked.

Concluding Remarks

Unfortunately, the current literature concerning beta−carotene supplementation and lung cancer incidence may best be summarized as inconclusive. Ultimately, longer follow-up periods and additional controlled intervention trials will be necessary to ascertain the effects of carotenoid supplementation on lung cancer development. In the meantime, no public health measures may be recommended regarding beta−carotene supplementation for lung cancer prevention, although health care providers should continue to encourage adequate fruit and vegetable intake.

Until the bewildering results of the CARET and ATBC trials are explained from basic science and epidemiologic standpoints, the optimal manner to prevent lung cancer shall remain the traditional triad of smoking cessation, smoking prevention, and elimination of hazardous occupational exposures such as asbestos[15]. Indeed, the puzzling relationship between carotenoid intake and lung cancer is a lucid example of the intricate and often obscure relationship between nutrition and oncogenesis.

References

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