Antioxidant Vitamins E and C and Risk of Alzheimer’s Disease

Age-related neurodegenerative disorders are increasing rapidly. Alzheimer’s disease is the most common cause of dementia associated with aging. A recent study has examined the role of vitamins E and C in a prospective epidemiologic cohort study and suggested that they might protect against Alzheimer’s disease.

Key Words: antioxidant, Alzheimer’s disease, neurocognition, aging

Alzheimer’s disease (AD) is characterized by regional neuronal degeneration, synaptic loss, and the presence of neurofibrillary tangles and senile plaques. Neurofibrillary tangles are aggregates of hyperphosphorylated microtubular tau protein, whereas senile plaques are complex extracellular lesions composed of a core containing β-amyloid (Aβ) surrounded by activated microglia, fibrillary astrocytes, and dystrophic neurites. AD is the most common cause of dementia in North America and Europe, accounting for one-half to two-thirds of all cases of dementia. The prevalence of AD varies from approximately 3% in persons aged 65 years to almost 50% in those over 85 years. AD has the potential to become the most overwhelming public health concern of this century owing to increasing life expectancy and growth in the aging population. The estimated cost of AD is at least $100 billion per year. Based on a recent study by Koppel and the Alzheimer’s Association in 2002, the projected cost of AD to American businesses will be more than $61 billion, twice the amount calculated just 4 years ago. With a growing elderly population, the cost of AD will increase almost fourfold in the next few decades. The report, commissioned by the Alzheimer’s Association, warns that the cost to U.S. businesses and the nation will continue to soar as baby boomers hit the highest-risk age for developing the disease. The cost of AD is exceeded only by heart disease and cancer. The costs for families, government, and business, if no preventive measurements and new therapies begin soon, will be unsustainable. Thus, recognition of the early symptoms of AD and initiation of even modestly effective interventions to prevent or delay onset are urgently needed to alleviate the growing economic and societal burden associated with AD (Figure 1).

A decade of research has suggested that reactive oxygen species (ROS) may contribute to the neuronal damage in AD. Some consider oxidative damage to be one of the early markers of neuronal dysfunction in AD. Many support the hypothesis that with advancing age comes increased production of ROS and diminished capacity of the body to protect against ROS, which may consequently lead to an increased oxidizing cellular environment. In vitro studies have reported a strong correlation between Aβ and generation of free radicals. Because increased production and deposition of Aβ are early events in the pathogenesis of AD that precede other changes such as the formation of tau, amyloid production and deposition may be associated with increased oxidative stress. Hence, the presence of a higher concentration of antioxidants may provide protection to neurons and preserve cognitive function. Other researchers, however, have measured plasma levels of 8-epiPGF2α as a marker of oxidation, and did not detect alterations in oxidative stress with aging or in AD. Thus, even though Aβ may cause neuronal toxicity via free radical–induced insult, other mechanisms are proposed to be involved in the pathogenesis of AD including inflammation.

Aβ can activate inflammatory pathways by enhancing the microglial secretion of inflammatory cytokines such as interleukin (IL)-1β and IL-6. Supporting a possible role of inflammation in the pathogenesis of AD, epidemiologic studies strongly suggest that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of developing AD. Using peripheral levels of C-reactive protein (CRP) as a marker of general inflammation, a recent study found that men in the upper three quartiles of plasma CRP had a significant threefold increased risk for all dementias combined, AD, and vascular dementia, compared with men in the lowest quartile. Recent animal studies, using orally administered ibuprofen for 6 months, also lend new experimental support to the theory that NSAIDs may be useful to the

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treatment of AD. Therefore, treatment of persons at risk of AD with anti-inflammatory drugs or nutrients that affect the inflammatory response may be beneficial. For example, vitamin E may affect the inflammatory response in the central nervous system and at the peripheral level by modulating inflammatory components that may be associated with AD. At present, various studies are seeking to determine whether using vitamin E, a common NSAID drug, or a selective cyclooxygenase-2 (COX-2) inhibitor can help delay the onset of AD in individuals with mild cognitive impairment. Simultaneous administration of vitamin E constitutes a novel approach to down-regulate expression or render COX-2 more sensitive to inhibition by NSAIDs.

Vitamin E deficiency can cause neurologic dysfunction, but the underlying molecular mechanisms remain unclear. Because of its antioxidant properties, vitamin E (α-tocopherol) may play an important role in preventing diseases associated with oxidative stress. Hence, a beneficial effect of vitamin E in reducing the risk of AD could be mediated by an antioxidant effect. However, other novel mechanisms of vitamin E action involving modulation of cellular signaling and transcriptional regulation may be relevant to an understanding of vitamin E’s effects on brain function. The role of vitamin E would be significantly underestimated if only its antioxidant properties were considered. Vitamin E has been shown to inhibit different key events in inflammation and signaling cascades such as influencing the phosphorylation state of protein kinase C, a key player in the signaling of cytokines, which may be relevant to AD. Another antioxidant, vitamin C (ascorbic acid), participates in several enzymatic reactions essential to the synthesis of catecholamines. There is considerable evidence that medications or vitamins that increase the levels of brain catecholamines and protect against oxidative damage may reduce the neuronal damage and slow the progression of AD.

Various epidemiologic studies have reported that dietary intake of antioxidants vitamins E and C, especially vitamin E, is associated with a lower risk of incident AD. Some studies reported that vitamin C supplement use was related to lower risk of AD; however, other studies did not support previous association between combined use of vitamin E and C supplements and lower risk of AD. Recently, a series of reports on vitamin E intake and dementia encouraged investigators conducting current clinical trials to test the effectiveness of vitamin E and other antioxidants in preventing or postponing cognitive decline and AD. These recent publications found a significant association between vitamin E intake and cognitive decline and dementia. A diet that includes whole-grain cereal for breakfast, a sandwich with whole-grain bread for lunch, and a dinner including a green leafy salad sprinkled with nuts, for example, would contain levels of vitamin E consumed by participants with the highest vitamin E intake in these studies.

Engelhart and colleagues, to assess the effects of antioxidants on cognitive function, addressed the role of antioxidants in the context of primary prevention; they suggested that a diet rich in foods containing high amounts of vitamins E and C may help to protect against AD. This study, conducted in the Netherlands, collected data on 5395 men and women, who were at least 55 years of age, who were participants in the population-based Rotterdam Study, and who were free of dementia at baseline.
After a mean follow-up of 6 years, there were 197 cases of dementia; 146 of these cases were diagnosed as AD. Data were adjusted for age, sex, baseline Mini-Mental State Examination score, alcohol intake, education, smoking, pack-years of smoking, body mass index, total energy intake, presence of carotid plaques, and the use of antioxidant supplements. After this adjustment, the researchers found that a high dietary intake of vitamin C and vitamin E was associated with a reduced risk of AD and this relationship was strongest among current smokers (Table 1).

Persons in the highest tertile of vitamin E intake from food (>15.5 mg/day) were 43% less likely to develop AD. These findings may reflect a cumulative benefit of antioxidant intake over a long period. The study also reported that vitamin E in the form of supplements was surprisingly not associated with a reduction in the risk of AD. A few years ago, a randomized controlled trial of supplemental vitamin E performed in patients with AD suggested that vitamin E at a dose of 1000 IU given twice daily to patients with moderately severe cognitive impairment slowed the progression of the disease and delayed the time to nursing home placement. Vitamin E supplementation in patients with AD delayed important dementia milestones, such as patients’ institutionalization or progression to severe dementia by approximately 7 months.

There is no apparent explanation for this noticeable divergence in the protective effect of vitamin intake from dietary sources as opposed to from supplement use. Studies on supplement use are more prone to bias because people who use supplements may have more health problems and more healthy behaviors. In addition, various other factors could be important modifiers of supplement effects, such as the length of time taking the supplement, constancy, amount, purity and type of preparation, and the composition of the mixture. An important concern of this study is perhaps the potential influence of the preclinical illness on either diet or supplement use, or on the way the patients reported their intake. For example, a patient who has problems remembering recent events might not accurately report recent dietary intake and supplement use. Alternatively, a patient who recognized signs of a decline in memory might be more likely to begin taking supplements. Early symptoms of developing dementia might be sufficient reason to precipitate supplement use or an improved diet; on the contrary, the nature of the illness might lead to a reversal of such reasonable behavior as the illness progresses. These uncertainties highlight the great difficulty inherent in observational studies that depend on recall of information for estimation of risk factor exposures for illnesses that have a long course, which could cause alterations in brain functions that influence behaviors, communication, memory, and other cognitive activity. Measurement of blood levels of nutrients can reduce some of the limitations underlying the validity of these studies.

Another concern in this study is that enrolled subjects were young, 55 years of age at baseline. The low incidence rates of dementia reported reflect the age of the population selected. Incidence rates for dementia are quite low until approximately 60 years; after 65 years rates generally double every 5 to 8 years of increasing age. In this study, nonsmokers were found to obtain no benefit from antioxidants. Smoking increases the formation of free radicals and oxidative stress. More than 20% of the subjects enrolled in this cohort were current smokers and analyses were stratified to address a possible interaction of smoking and nutrient intake. The analyses showed a strong association between vitamin E and AD among smokers, but no association among those who never smoked. Various factors—the predominately low-risk population enrolled in the study, subjects were ≥55 years of age, and a relatively short period (6 years) of follow-up—may have contributed to lack of association reported between vitamin E and dementia among those who never smoked. A source of potential bias in this study is the use of a food frequency questionnaire (FFQ) to estimate dietary intake of antioxidants. This methodology requires that the patient recall and report the consumption of a large number of individually specified foods (178 items); the FFQ routinely asks about usual serving sizes and frequency of consumption in specified intervals during a general time period. Therefore, FFQ responses require continuous motivation, attention, and memory. Patients with more preserved functional ability might therefore be expected to provide more accurate FFQ data concerning foods rich in antioxidant nutrients. Declines in attention and memory function that precede AD, but are not yet evident, could also influence estimates of food intake on the FFQ. Dietary assessment was performed only once and may not precisely reflect the participant’s long-term dietary habits. The study also reported no association of vitamin E intake on AD in

Table 1. Effect of Vitamin E on Risk of AD after 6 Years of Follow-up

<table>
<thead>
<tr>
<th>Dietary Intake of:</th>
<th>Association between Antioxidants Intake and Risk of AD (RR)</th>
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<tbody>
<tr>
<td></td>
<td>Smokers</td>
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<tr>
<td>Vitamin E</td>
<td>0.58</td>
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<tr>
<td>Vitamin C</td>
<td>0.65</td>
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<tr>
<td>β-carotene</td>
<td>0.49</td>
</tr>
<tr>
<td>Flavonoids</td>
<td>0.54</td>
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Participants = 5395, dementia = 197, AD = 146, AD = Alzheimer’s disease, RR = relative risk.
those individuals with the apolipoprotein E4 allele (APOE) genotype. However, this genotype is a risk factor for late development of AD. In addition, subjects with APOE may have a positive family history of AD, and may consequently be diagnosed at a younger age; this would affect the in

definition of the underlying neurodegenerative process on development of AD or the preclinical cognitive manifestations of the underlying neurodegenerative process on behavior. These inaccuracies are of potential concern in this type of study because they can introduce systematic measurement error and contribute to residual confounding for which investigators are unable to correct.

Despite the potential problems, the findings reported by this study are important and interesting. The suggestion that antioxidants might have beneficial effects on the underlying changes associated with the pathogenesis of AD is very important and supports the promotion of higher dietary intake of antioxidant-rich foods. Well-designed intervention trials, as well as observational investigations based on larger cohorts, with longer study duration, and using multiple methodologies to assess molecular and antioxidant effects, are necessary to test the hypothesis.


The Relationship between Obesity and Breast Cancer Risk and Mortality

Obesity is an established risk factor for postmenopausal, but not premenopausal, development of breast cancer. Evidence for a positive association between obesity and breast cancer mortality is mounting. Avoiding adult weight gain and maintaining a healthy body weight may contribute importantly to decreasing breast cancer risk and mortality, especially in postmenopausal women.

Key Words: obesity, BMI, breast cancer risk, breast cancer mortality

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Obesity is an established risk factor for breast cancer in postmenopausal women, but not in premenopausal women. Few studies have assessed the relationship between obesity and breast cancer mortality. Obesity has been shown to increase breast cancer mortality in women after menopause in the Nurses’ Health Study by Huang et al. and in a large Norwegian study by Tretli. The recently published study in Cancer Causes and Control by Petrelli et al. strongly supports these findings. The authors showed that breast cancer mortality rates increased continually and substantially with increasing body mass index (BMI, kg/m²) in postmenopausal women (relative risk [RR] = 3.08, 95% confidence interval [CI] = 2.09–4.51 for BMI ≥40 compared with BMI 18.5–20.49 [p for trend <0.0001]). The authors used a sample of 424,168 eligible women who were postmenopausal and cancer-free at baseline. These women were selected from 676,306 female participants in the Cancer Prevention Study II, a prospective mortality study of American men and women begun by the American Cancer Society in 1982. After 14 years of follow-up, 2,852 breast cancer deaths were observed. Cox proportional hazards modeling was used to estimate relative risk and to control for potential confounders such as age, family history, and other lifestyle factors.