Vitamin C, Vitamin E and Beta-Carotene in Relation to Common Cold Incidence in Male Smokers

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Abstract

We evaluated the role of dietary vitamin C, vitamin E, and beta-carotene, as well as long-term vitamin E and beta-carotene supplementation, on the incidence of common cold episodes. A cohort of 21,796 male smokers was drawn from the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, which examined the effects of 50 mg per day vitamin E and 20 mg per day beta-carotene on lung cancer. Diet and background characteristics were recorded at the study entry, and subjects were queried three times per year on common cold episodes. We modeled the total number of colds during a 4-year follow-up period with Poisson regression, adjusting for covariates of dietary intake. Dietary vitamins C and E and beta-carotene had no meaningful association with common cold incidence. Long-term vitamin E and beta-carotene supplementation had no overall effect. Among subjects 65 years of age or older, the incidence of colds was slightly lower in the vitamin E group (RR = 0.95; 95% CI = 0.90–1.00); this reduction was greatest among older city dwellers who smoked fewer than 15 cigarettes per day (RR = 0.72; 95% CI = 0.62–0.83). In this male smoking population, vitamins C and E and beta-carotene had no overall association with the incidence of common cold episodes.

Key Words: alcohol, alpha-tocopherol, ascorbic acid, beta-carotene, fruit, smoking, upper respiratory infections, vegetables

Introduction

Several reports have indicated that vitamin C may affect the functions of phagocytes, the proliferation of T-lymphocytes, and the production of interferon [1–3]. Vitamin E has been found to affect various parts of the immune system [4,5], but two studies found reduced bactericidal activity of phagocytes in subjects given high doses of vitamin E [6,7]. A few studies have reported effects by beta-carotene on certain immune parameters [8].

In 1971 Pauling [9] carried out a meta-analysis of four placebo-controlled studies and concluded that there was strong evidence indicating that vitamin C supplementation decreased common cold incidence (P = 0.003). Since then, the six largest trials have found no preventive effect from ≥1 gm per day vitamin C supplementation on common cold incidence, with a pooled relative risk (RR) of 0.99 (95% CI = 0.93–1.04) [10]. Nevertheless, in four trials with British males [11–14], a modest reduction in common cold incidence was found in vitamin C supplementation groups, with a pooled RR of 0.70 (95% CI = 0.60–0.81) [10]. Other trials have also found lower common cold incidence in vitamin C groups [15,16]. The severity and duration of common cold symptoms has quite consistently been reduced by regular large-dose vitamin C supplementation, but the benefit has been modest [16–20].

Few studies have examined the role of vitamin E and beta-carotene in infectious diseases. In a retrospective study of healthy elderly subjects, the number of preceding unspecified infections was higher among subjects having low plasma vitamin E levels [21]. Two trials with elderly subjects found no effect on the total number of infections with either 200 or 400 mg per day of vitamin E [22] or 30 mg per day of vitamin E along with other vitamins [23]. In two further small trials with elderly subjects, the total number of infections was 30% lower when they were given 60–800 mg per day vitamin E [5], or the combination of 15 mg per day vitamin E, 6 mg per day beta-carotene, and 120 mg vitamin C [24]. Previously we found that vitamin E and beta-carotene supplementation had no effect on the incidence of tuberculosis in the Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) Study cohort [25].

The purpose of the present study is to find out whether dietary vitamin C or E, dietary beta-carotene, or long-term supplementation with vitamin E or beta-carotene affects the incidence of common cold episodes.

Subjects and Methods

Subjects
The methods of the ATBC Study, designed to examine the effects of vitamin E, alpha-tocopherol (50 mg per day), and beta-carotene (20 mg per day) on the incidence of lung cancer and other cancers, have been described in detail elsewhere [26,27]. In brief, the trial participants were recruited in 1985–1988 from the total male population 50–69 years of age living in southwestern Finland (N = 290,406). To be eligible, participants had to smoke ≥5 cigarettes per day at entry; potential participants were excluded if they had severe medical problems or if they used supplemental vitamin E, vitamin A, or beta-carotene in excess of predefined doses. The eligible participants (N = 29,133) were randomized to one of four intervention groups of the same size and administered placebo, alpha-tocopherol, beta-carotene, or both nutrients together. The intervention continued for 5–8 years (median 6.1 years) until 1993, with three follow-up visits annually to the local study center. The trial was approved by the institutional review boards of the participating institutions, and all subjects gave written informed consent. Compliance in the study was high; some 90% of subjects took more than 90% of their prescribed capsules during their active participation in the trial; there were no differences in capsule consumption among the intervention groups [26].

Baseline Characteristics and Dietary Assessment
At baseline, before randomization, the men completed a questionnaire on medical and smoking histories and general background characteristics.

At the first baseline visit subjects were given a detailed dietary history questionnaire for completion at home [28], and 2 weeks later the questionnaire was returned and reviewed. The questionnaire included a color picture booklet and asked about portion sizes for 276 common foods and mixed dishes and the usual frequency of their consumption over the previous year. Also, consumption of specific alcoholic beverages was requested and transformed to mean alcohol intake per day. The daily dietary intakes of vitamins C and E and beta-carotene were calculated using the National Public Health Institute food composition database [29], which includes correction coefficients for vitamin C destroyed during food preparation. The reproducibility and validity of the food frequency questionnaire used in the ATBC Study were previously evaluated [28].

The use of vitamin C supplements by subjects' own initiative was inquired about at each of the follow-up visits. For subjects reporting use of vitamin C supplements on the first follow-up visit (N = 1,949), the median dose was 75 mg per day. Regular vitamin C supplementation was rare (<1%), and the doses were usually small. Therefore, we ignored supplemental vitamin C when calculating the dietary vitamin C intakes.

Outcome and Follow-Up Time
At each follow-up visit the subjects were asked about their health status, including the question, "Have you had the common cold since the previous visit, and if so, how many times?" The occurrence of "other upper respiratory tract infection" and "acute bronchitis" was asked in parallel with the common cold question. These self-reported illnesses were not further verified.

There is substantial seasonal variation in the occurrence of the common cold, and therefore full-year follow-up periods were used to cover all seasons. Because the shortest scheduled intervention in the ATBC Study was 4.7 years, we used a 4-year follow-up period starting from the randomization day in the main analysis; 21,796 subjects participated at the 4-year visit. We calculated the total number of colds per person (cumulative incidence) during the 4-year period as the main outcome. Subjects who did not participate at the 4-year follow-up visit (N = 7,337) did not differ substantially from those who participated at the 4-year visit by their mean age (58.3 *vs* 57.5 years) or mean number of cigarettes smoked (21.1 *vs* 20.2 per day). When pertinent, the common cold incidence was also calculated over the first, second, third, and fourth follow-up year.

Statistical Methods
We limited the analysis of the association of cumulative common cold incidence with dietary intakes of vitamins C and E and beta-carotene and with consumption of fruits and vegetables to men in the placebo arm of the trial. Of 5,450 placebo group men with common cold data through the 4-year follow-up, 280 men were missing data on diet, leaving 5,170 men for the analysis on diet. We modeled these associations using Poisson regression, including relevant baseline characteristics. We calculated the adjusted rate ratio as an estimator of relative risk and the likelihood ratio-based 95% confidence interval (95% CI), using the SAS PROC GENMOD program. Alcohol was included as a dichotomous yes-or-no variable; the other potential confounding factors were categorized as in Table 1.

We also used the Poisson regression model to examine the effects of supplementation on the cumulative incidence of colds. The supplementation assignments were based on a two-by-two factorial design, permitting assessment of vitamin E and beta-carotene effects independently (after demonstrating that these supplementations had no interaction). As to supplementation, the analyses were carried out following the intention-to-treat principle, but the outcome was available only for those subjects who participated in the follow-up visits over 4 years.

To analyze the seasonal variation in the effect of vitamin E on the common cold incidence in the 4-year period, we modeled the number of colds reported during the follow-up visits over 3-month ranges. At each follow-up visit the subjects reported the number of colds since the previous follow-up visit (*ie*, over the previous 4-month period).

Analyses were carried out using SAS (release 6.12, SAS Institute, Cary, NC) and Stata (release 7, Stata Corp, College Station, TX).

Results

On average, there were 0.8 self-reported common cold episodes per person per year during the 4-year follow-up period. No colds during the 4-year period were reported by 16% of the subjects, one or two colds by 34%, and six colds or more by 20% of the subjects.

Age, smoking, coffee consumption, and education had weak associations with common cold incidence in the placebo arm of the trial (Table 1). Being an abstainer from alcohol was associated with a slightly lower incidence of colds compared with those using any alcohol (RR = 0.92, 95% CI = 0.87–0.96); the amount of alcohol had no further effect. With only 1 year of follow-up (N = 6,122), the estimates did not substantially differ, but the confidence intervals were wider (not shown).

Common cold episodes were less frequent among those having low dietary intake of vitamin C compared with those with high intake (Table 2). Similar results were found when the analysis was restricted to subjects not consuming any vitamin C supplements during the 4-year follow-up (N = 3,998) (data not shown). Dietary vitamin E and beta-carotene intake and the consumption of fruits and vegetables were also positively associated with the incidence of colds (Table 2).

Among all study subjects, long-term vitamin E and beta-carotene supplementation had no effect on the common cold incidence (Table 3).

Vitamin E supplementation was associated with a slightly lower incidence of common cold episodes during the 4-year period only among subjects 65 years of age or older (RR = 0.95; 95% CI = 0.90–1.00). Age did not modify the effect of beta-carotene. Vitamin E and beta-carotene supplementation effects were not modified by smoking, alcohol consumption, or city dwelling (data not shown).

Exploratory analyses among subjects 65 years of age or older revealed that smoking and residential neighborhood further modified the effect of vitamin E. Among city dwellers smoking 5–14 cigarettes per day, the risk of colds was reduced in the vitamin E group (RR = 0.72; 95% CI = 0.62–0.83), whereas vitamin E had no effect among subjects living in smaller neighborhoods or smoking ≥15 cigarettes per day (Table 4). Vitamin E supplementation had essentially a similar effect among the older city dwellers smoking 5–9 cigarettes per day (RR = 0.69; 95% CI = 0.56–0.86; N = 114) and those smoking 10–14 cigarettes per day (RR = 0.75; 95% CI = 0.61–0.91; N = 147).

To analyze whether the period of supplementation affects the role of vitamin E in the older city dwellers smoking 5–14 cigarettes per day (N = 261), the 4 consecutive years of follow-up were analyzed independently. The risks of colds were RR = 0.73 (95% CI = 0.55–0.96), RR = 0.76 (95% CI = 0.58–1.00), RR = 0.66 (95% CI = 0.48–0.89), and RR = 0.72 (95% CI = 0.53–0.97) in the 4 consecutive years.

Seasonal variation in the effect of vitamin E was analyzed in the older city dwellers smoking 5–14 cigarettes per day (N = 261) over the 4-year follow-up. Common cold incidence was considerably lower in the summer compared with that in the winter (not shown). The number of colds reported in the July-through-September follow-up visits was not different between vitamin E and non-vitamin E groups (RR = 0.89; 95% CI = 0.63–1.25). In the other 3-month periods, consistent differences between the two supplementation groups were found: October through December, RR = 0.59; 95% CI = 0.42–0.81; January through March, RR = 0.71; 95% CI = 0.55–0.91; and April through June, RR = 0.78; 95% CI = 0.60–1.01.

The 4-year cumulative incidence of common cold episodes was overdispersed compared with the ideal Poisson distribution, and therefore we also carried out negative binomial regression analysis (nbreg in Stata) in the group of the older city dwellers who smoked 5–14 cigarettes per day (N = 261). The confidence interval (RR = 0.72; 95% CI = 0.57–0.92) was somewhat wider than in the Poisson model.

Discussion

We found no protective association between dietary vitamin C or E or beta-carotene and the incidence of self-reported colds. Vitamin E supplementation slightly decreased common cold incidence among the older subjects, but beta-carotene had no effects.

Although the largest vitamin C trials found no effects on common cold incidence [10], several studies in the United Kingdom with male subjects suggest that low intake of vitamin C might increase the incidence of colds [10–14]. Among our subjects, low dietary intake of vitamin C was not associated with increased incidence of colds; the incidence was instead slightly lower (Table 2), perhaps as a result of residual confounding. In the United Kingdom trials [11–14], the subjects were schoolchildren or students, whereas all of our subjects were at least 50 years of age. Thus, low vitamin C intake might increase the risk of colds only in younger people.

High intake of fruits and vegetables has been found to be associated with a lower incidence of influenza-like symptoms in Japanese children [30] and with a lower incidence of acute respiratory symptoms in Australian subjects with a wide age range [31]. Students in the United States had fewer colds when given one apple per day in a 1-year trial [32]. In young adults, orange juice reduced the incidence of respiratory symptoms of nasally inoculated rubella virus infection and the incidence of experimental rhinovirus infection [33,34]. To our knowledge, no previous studies have examined the association between dietary vitamin C or E or beta-carotene and the incidence of colds or other respiratory infections. In our subjects, high intake of fruits and vegetables was not associated with a decreased common cold incidence, and similar negative findings were seen for dietary vitamin E and beta-carotene.

Long-term vitamin E and beta-carotene supplementation had no overall effect on the incidence of colds, but the risk of colds was slightly reduced among subjects 65 years of age or older with vitamin E supplementation (Table 3). Smoking and residential area seemed to modify the effect of vitamin E among these older subjects, and incidence of the common cold was reduced only among the older city dwellers smoking 5–14 cigarettes per day (Table 4). The difference in the number of colds between vitamin E and non-vitamin E groups in the small group of older subjects may be a biological effect or may have arisen by chance from a series of subgroup analyses. Still, it is noteworthy that the three factors characterizing the small subgroup have plausible effects on the vitamin E-common cold relationship. There is age-related decline in various immune functions [35]; cigarette smoking may modify respiratory infections [36]; and living in a crowded city is associated with greater air pollution, which also may affect respiratory infections [37].

The incidence of colds in our study, 0.8 per year, is consistent with previous estimates in the same age range [38,39]. No virologic or serologic tests were carried out in our study to explore the nature of possible viruses causing the self-reported colds. It is the subjective symptoms rather than positive laboratory findings that lead a person to seek medical attention and obtain sick leave, and so in this respect the subjective outcome is more relevant for public health purposes. Nevertheless, differences in the subjective perception of colds is a potential source of bias in our analysis of dietary effects, whereas our trial results on supplementation are less affected by this as a result of randomization.

Our study may be criticized because the outcome, self-reported colds, contains a variety of viral respiratory episodes of different severity, but may also include certain acute allergic symptoms. The heterogeneity of outcome, however, does not seem to affect our conclusions of the trial results. In subjects less than 65 years of age, vitamin E had no effect with a very narrow confidence interval, and the same was found for beta-carotene in all subjects. To assume that among these subjects vitamin E or beta-carotene might decrease the incidence of certain specific kinds of colds (*eg*, severe colds or colds caused by a certain virus) would require that the substance exactly and equivalently increase the incidence of colds in the complementary group (*eg*, mild colds or colds caused by other viruses). Such a possibility seems highly improbable.

The heterogeneity of outcome also seems not to be critical for our conclusions in the small group of subjects among whom vitamin E appeared to reduce the incidence of colds. Although part of the self-reported colds might be acute hay fever-type reactions, the observed pattern of seasonal variation is inconsistent with vitamin E having effects on summertime allergies in particular. The magnitude of effect by vitamin E may vary with different kinds of cold episodes. This would restrict the generalization of observed estimate, but is highly unlikely to generate the difference between vitamin E and non-vitamin E groups as an artificial effect. In any case, the observed effect is rather small and seems to have no immediate practical importance, yet it seems to warrant further investigations.

Although vitamins C and E may affect susceptibility to respiratory infections in restricted groups of subjects under special circumstances, the results of the present analysis and the findings of several other studies indicate that such subpopulations are not large in the Western countries.

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TABLE 1. Relative Risk of the Common Cold in Relation to Baseline Characteristics during 4-Year Follow-Up, ATBC Study 1985–1992, the Placebo Arm of the Trial (N = 5,170)

Variable	Proportion (%)	Colds/year (mean)	Relative risk of colds[a]	
			RR	(95% CI)
Age (years)				
50-54	38	0.92	1.00	ref.
55-59	32	0.82	0.90	(0.87-0.93)
60-64	21	0.80	0.90	(0.86-0.94)
65-69	9	0.74	0.84	(0.78-0.89)
Cigarettes per day				
≤14	20	0.82	1.00	ref.
15-24	49	0.84	1.01	(0.97-1.05)
25-34	24	0.85	1.01	(0.97-1.06)
≥35	7	0.98	1.14	(1.07-1.22)
Alcohol (gm/day)				
0	11	0.76	0.92	(0.87-0.97)
>0-14	48	0.84	1.00	ref.
15-29	23	0.90	1.04	(1.00-1.09)
≥30	18	0.88	0.99	(0.95-1.03)
Coffee intake (dl/day)				
<3	14	0.92	1.00	ref.
3-5	37	0.86	0.94	(0.90-0.98)
≥6	49	0.82	0.88	(0.84-0.92)
Education (years at school)				
≤6	77	0.83	1.00	ref.
7-9	15	0.90	1.05	(1.01-1.10)
≥10	8	0.93	1.08	(1.02-1.15)
Marital status				
Married	83	0.85	1.00	ref.
Not married	17	0.85	1.00	(0.96-1.04)
Residential area				
City (>50,000 inhabitants)	43	0.87	1.00	ref.
Town or countryside	57	0.84	0.99	(0.96-1.02)
Employed				
Yes	62	0.88	1.00	ref.
No	38	0.79	0.96	(0.92-1.00)

[a] Poisson regression model; for each variable, adjustment by all other variables in the table. Subjects with missing data on diet (N = 280) were excluded.

TABLE 2. Relative Risk of the Common Cold in Relation to Baseline Dietary Vitamin C, Vitamin E, and Beta-Carotene Intake, and Fruit and Vegetable Consumption during 4-Year Follow-Up, ATBC Study 1985–1992, the Placebo Arm of the Trial (N = 5,170)

Intake Quartile	Vitamin C		Vitamin E		Beta-Carotene		Fruits and vegetables	
	Median Intake (mg/day)	Relative Risk of Colds[a] RR (95% CI)	Median Intake (mg/day)	Relative Risk of Colds[a] RR (95% CI)	Median Intake (mg/day)	Relative Risk of Colds[a] RR (95% CI)	Median Intake (g/day)	Relative Risk of Colds[a] RR (95% CI)
1 (Low)	54	0.94 (0.90-0.98)	6.9	0.90 (0.86-0.94)	0.9	0.86 (0.82-0.89)	62	0.96 (0.91-1.00)
2	80	0.94 (0.90-0.98)	9.4	0.96 (0.92-1.00)	1.4	0.95 (0.90-0.98)	124	0.92 (0.88-0.96)
3	105	1.03 (0.99-1.08)	12.3	0.94 (0.90-0.98)	2.2	0.92 (0.88-0.96)	187	0.99 (0.95-1.03)
4 (High)	150	1.00 ref.	18.3	1.00 ref.	3.8	1.00 ref.	304	1.00 ref.

[a] Poisson regression model; adjusted for age, smoking, alcohol and coffee consumption, education, and employment. Subjects with missing data on diet (N = 280) were excluded

TABLE 3. Relative Risk of the Common Cold by Vitamin E and Beta-Carotene Supplementation during 4-Year Follow-Up, ATBC Study 1985–1992

	No. of Subjects	Supplementation		Relative Risk of Colds[a]	
		Colds/Year	Colds/Year	RR	(95% CI)
		Vitamin E	No vitamin E		
All subjects	21,796	0.843	0.848	0.99	(0.98-1.01)
Age (years)					
<65	19,791	0.856	0.858	1.00	(0.98-1.01)
≥65	2,005	0.71	0.75	0.95	(0.90-1.00)
		beta-Carotene	No beta-carotene		
All subjects	21,796	0.847	0.844	1.00	(0.99-1.02)
Age (years)					
<65	19,791	0.859	0.856	1.00	(0.99-1.02)
≥65	2,005	0.73	0.73	1.00	(0.95-1.05)

[a] Poisson regression model comparing intervention to no intervention.

TABLE 4. Relative Risk of the Common Cold in Relation to Vitamin E Supplementation during 4-Year Follow-Up in Subjects 65 Years of Age or More, ATBC Study 1985–1992

	No of. Subjects	Supplementation		Relative Risk of Colds[a]	
		Vitamin E	No vitamin E		
		Colds/Year	Colds/Year	RR	(95% CI)
Smoking 5-14 cigarettes/day ***and*** living in a city	261	0.63	0.87	0.72	(0.62-0.83)
Smoking ≥15 cigarettes/day ***or*** living in a small neighbourhood	1,743	0.72	0.73	0.99	(0.94-1.05)

[a] Poisson regression model comparing intervention to no intervention.
One subject is excluded because of missing data on residential area.