Vitamin E and Beta-Carotene Supplementation and Hospital-Treated Pneumonia Incidence in Male Smokers*

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Background: **Vitamin E and beta-carotene affect various measures of immune function and accordingly might influence the predisposition of humans to infections. However, only few controlled trials have tested this hypothesis.**
Study objective: **To examine whether vitamin E or beta-carotene supplementation affects the risk of pneumonia in a controlled trial.**
Design and setting: **The Alpha-Tocopherol Beta-Carotene Cancer Prevention (ATBC) study, a randomized, double-blind, placebo-controlled trial that examined the effects of vitamin E, 50 mg/d, and beta-carotene, 20 mg/d, on lung cancer using a 2 × 2 factorial design. The trial was conducted in the general community in southwestern Finland in 1985 to 1993; the intervention lasted for 6.1 years (median). The hypothesis being tested in the present study was formulated after the trial was closed.**
Participants: **ATBC study cohort of 29,133 men aged 50 to 69 years, who smoked at least five cigarettes per day, at baseline.**
Main outcome measure: **The first occurrence of hospital-treated pneumonia was retrieved from the national hospital discharge register (898 cases).**
Results: **Vitamin E supplementation had no overall effect on the incidence of pneumonia (relative risk [RR], 1.00; 95% confidence interval [CI], 0.88 to 1.14) nor had β-carotene supplementation (RR, 0.98; 95% CI, 0.85 to 1.11). Nevertheless, the age of smoking initiation was a highly significant modifying factor. Among subjects who had initiated smoking at a later age (≥ 21 years; n = 7,469 with 196 pneumonia cases), vitamin E supplementation decreased the risk of pneumonia (RR, 0.65; 95% CI, 0.49 to 0.86), whereas beta-carotene supplementation increased the risk (RR, 1.42; 95% CI, 1.07 to 1.89).**
Conclusions: **Data from this large controlled trial suggest that vitamin E and beta-carotene supplementation have no overall effect on the risk of hospital-treated pneumonia in older male smokers, but our subgroup finding that vitamin E seemed to benefit subjects who initiated smoking at a later age warrants further investigation.** ***(CHEST 2004; 125:557–565)***

Key words: alcohol; alpha-tocopherol; antioxidants; body mass index; clinical trial; coffee; cohort study; community-acquired pneumonia; diet; risk factors

Abbreviations: ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention; CI = confidence interval; ICD = International Statistical Classification of Diseases, Injuries, and Causes of Death; OR = odds ratio; RR = relative risk

Animal studies[1–4] have shown that vitamin E supplementation increases resistance to various infections. Although several studies[5] indicate that vitamin E may have beneficial effects on various parts of the immune system in humans, other studies show no benefit[6–8] or even harmful effects of large doses.[9,10]

Only a few clinical studies have examined the effect of vitamin E supplementation on infectious disease outcomes, many of these trials being small

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and of short duration. Among patients in a chronic care facility, the incidence of respiratory and urinary tract infections was not affected by vitamin E, 200 mg/d or 400 mg/d.[11] Likewise, risk of respiratory and urinary tract infection was not affected by the combination of 15 mg/d of vitamin E with 6 mg/d of beta-carotene and 120 mg/d of vitamin C in subjects ≥ 65 old.[12,13] Also, 30 mg/d of vitamin E taken with other vitamins had no impact on unspecified infections among those ≥ 60 years old.[14] By contrast, a small trial of subjects ≥ 65 years reported 30% fewer unspecified infections among those administered 60 to 800 mg/d of vitamin E,[15] but the effect was not statistically significant. A recent study[16] with 652 subjects aged ≥ 60 years old found no effect by 200 mg/d of vitamin E on the incidence of respiratory infections, but the illness duration was unexpectedly increased by the vitamin. We have previously shown that supplementation with 50 mg/d of vitamin E had no impact on the incidence of tuberculosis or the common cold in male smokers.[17,18]

Available research also suggests that beta-carotene may influence the immune system.[19] We found no effect of 20 mg/d of beta-carotene on the incidence of tuberculosis or the common cold in male smokers in a controlled trial.[17,18] Also, no effect on the incidence of respiratory and urinary tract infection was found in a study of elderly patients treated with the combination of 6 mg/d of beta-carotene along with vitamins C and E.[12,13]

This article presents the effects of 6-year supplementation with vitamin E or beta-carotene on the incidence of hospital-treated pneumonia in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study cohort, a large, randomized, double-blind placebo-controlled trial testing primary prevention of lung cancer.

Materials and Methods

Study Participants and Intervention Groups

The rationale, design, and methods of the ATBC study examining the effects of vitamin E (dl-alpha-tocopheryl acetate, 50 mg/d) and beta-carotene (20 mg/d) on the incidence of lung cancer and other cancers have been described in detail.[20,21] In brief, the trial participants were recruited in 1985 to 1988 from the total male population aged 50 to 69 years living in southwestern Finland (n = 290,406). To be eligible, participants had to smoke at least five cigarettes per day at entry. Potential participants were excluded if they had medical problems that might limit long-term participation, or 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: placebo, alpha-tocopherol, beta-carotene, or alpha-tocopherol plus beta-carotene. The intervention continued for 5 to 8 years (median, 6.1 years) until April 30, 1993. The trial was approved by the institutional review boards of the participating institutions, and all subjects gave written informed consent. Compliance with supplementation was high: some 90% of the subjects took > 90% of their prescribed capsules during their active participation in the trial; there were no differences in capsule consumption among the intervention groups.[21]

Baseline Assessments and Smoking Data During Follow-up

At baseline prior to randomization, the men completed questionnaires on their medical and smoking histories and general background characteristics. Subjects were also asked whether they were employed or not. Subjects not working comprised a heterogeneous group that included age- and health-related retirees, as well as those unemployed for other reasons. A chest radiograph was obtained at baseline to exclude existing lung cancer, and was repeated every 28 months to enhance the ascertainment of lung cancer during the trial.[21]

At the first baseline visit, subjects were given a detailed dietary history questionnaire to be completed at home, and returned and reviewed at the second study visit 2 weeks later.[22] The questionnaire asked the usual frequency of the consumption of 276 common foods and mixed dishes over the previous 12 months, and included a color picture booklet for assessment of portion sizes. Also, consumption of specific alcoholic beverages was queried, providing average daily alcohol (ethanol) intake. The reproducibility and validity of the dietary questionnaire were previously evaluated.[22] The dietary intakes of vitamin E and beta-carotene were calculated using the food composition database of the National Public Health Institute.[23] Complete dietary data were not available for 2,022 participants, and these men were excluded from the dietary analysis.

There were three follow-up visits annually (*ie*, at 4-month intervals). At each follow-up visit, the subject was asked, "Have you been smoking since the previous visit?" with the following alternative responses provided: (1) no, (2) yes, but now I have quit, and (3) yes, continuously. Men who replied with either answer 1 or answer 2 were combined into one category: subjects who quit smoking prior to the follow-up visit.

Outcomes

The events for this study, the first hospital-treated pneumonia between randomization and April 30, 1993, were ascertained from the National Hospital Discharge Register using the unique personal identification number for linkage. The National Hospital Discharge Register covers inpatient visits from all public and private hospitals in Finland. It uses the codes of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD), the eighth edition (ICD-8) was used through the end of 1986, and the ninth edition (ICD-9) thereafter. Up to four diagnoses per each discharge are recorded, the primary diagnosis and three secondary diagnoses. The validity of the Finnish Hospital Discharge Register was examined from a random sample of 2,211 discharges.[24] The registered cause of hospitalization was compared with the medical records, and in 94.4% of the cases the same diagnosis was reached. In the category of diseases of the respiratory system, 94% of the diagnoses were verified, based on 135 discharge records.

For this study, pneumonia was defined by ICD-8 codes 480–486 and 471.0 and ICD-9 codes 480–485 and 487.0, and both primary and secondary diagnoses were accepted. There were 964 new cases of pneumonia during the trial: 345 cases (36%) with no discharge diagnoses other than pneumonia, and 619 cases (64%) with one or more other diseases concurrently with the pneumonia. In cases where both pneumonia and lung cancer (ICD code 162) were present in same discharge record

(n = 66 subjects), follow-up was censored at the date of the pneumonia diagnosis but the pneumonia was excluded, thus leaving 898 cases for the present analysis. Among 553 subjects, other diagnoses made concurrently with the pneumonia included, most commonly, other pulmonary diseases (n = 169) and diseases of the circulatory system (n = 238).

Of the 345 subjects who had pneumonia as the only hospital discharge diagnosis, 291 subjects (84%) had pneumonia of undefined etiology (ICD-8 codes 485.0 or 486.0, or ICD-9 code 485.9), and 16 subjects (5%) had pneumococcal pneumonia (ICD-8 code 481.9 or ICD-9 code 481.0). The etiology of pneumonia was undefined in 476 subjects (86%) of the 553 subjects with concurrent illnesses.

Statistical Analysis

Follow-up time for each participant began from the day of randomization, and continued until the date of first hospital discharge for pneumonia, death, or the end of the trial, April 30, 1993, whichever came first. The median follow-up time of the subjects in the present analysis was 5.8 years, and there was a total of 167,968 person-years of observation. Use of the Hospital Discharge Register allowed obtaining information on pneumonia in all study participants irrespective of whether they continued or dropped out of the trial.

The association between baseline characteristics, and dietary vitamin E and beta-carotene and pneumonia incidence was evaluated using proportional hazards regression analyses.[25] The relative risk (RR) and the 95% confidence interval (CI) of the RR were calculated using the PROC PHREG program of the SAS package of programs (release 8.1, SAS Institute; Cary, NC). The associations of baseline characteristics, presented in Table 1, with pneumonia incidence were studied in a model including simultaneously all the characteristics. The models on dietary intake of vitamin E and beta-carotene were adjusted for by those baseline characteristics that had substantial associations with the risk of pneumonia.

Effects of vitamin E and beta-carotene supplementation on pneumonia incidence were estimated through proportional hazards regression models. The 2×2 factorial design of the trial permitted assessment of the effects of vitamin E and beta-carotene independently after confirming no statistical interaction between the agents. Thus, one half of the trial participants were administered vitamin E and were compared with the other half not receiving vitamin E. Similarly, one half of the trial participants receiving beta-carotene were compared with the other half not being administered beta-carotene. No covariates were included in the models analyzing the treatment effects since the treatment groups originated from randomization and were balanced (data not shown).

To test the statistical significance of interaction between supplementation and potential modifying factors, the supplementation groups and modifying factor groups were first added to the regression model. The statistical significance of the interaction was thereafter calculated from the change in $-2 \times \log(\text{likelihood})$ when the cross-product interaction term for supplementation and the modifying factor was added to the model.

When observing that age at smoking initiation seemed to interact with the supplementation, we explored which age would be the most functional cut-point to split the young and old smoking initiators, and 21 years was found to be the best cut-point. Age at smoking initiation was also used as a continuous variable since interaction with a continuous variable refutes the possibility that explorative selection of cut-point would cause a spurious interaction. Two-tailed p values were used.

Smoking status at the occurrence of pneumonia was based on data from the follow-up visit immediately preceding pneumonia: 0 to 4 months earlier. A pneumonia case was considered a dropout from the trial if the subject missed the follow-up visit immediately preceding pneumonia and all subsequent visits after pneumonia. Four pneumonia cases (three continuous smokers and one quitter) continued in the study after their hospitalization for pneumonia but missed the visit immediately preceding diagnosis; their smoking status was derived from the next prior follow-up visit and it remained the same after the pneumonia episode. The odds ratio (OR) and the corresponding 95% CI were estimated through logistic regression models (SAS Institute).

Results

Characteristics of the trial participants at baseline are shown in Table 1. There were 898 cases of hospital-diagnosed pneumonia during the trial period, representing a mean rate of 5.3 cases per 1,000 person-years of follow-up.

Older men and the leanest men were at significantly elevated risk of pneumonia (Table 1). Smoking more cigarettes daily, and more cumulative years as a smoker, were associated with higher pneumonia rates compared with less smoking, while age of smoking initiation did not affect risk. Being an abstainer, or consuming > 60 g/d of alcohol daily were both associated with increased pneumonia occurrence compared with subjects consuming low amounts of alcohol, and drinking > 300 mL of coffee per day was associated with a lower risk compared with subjects drinking less coffee (Table 1). Education, marital status, and residential neighborhood were not associated with pneumonia, while not working was associated with an elevated risk. The associations between the background characteristics and the risk of pneumonia were similar when the analysis included only the pneumonia cases without any concurrent diseases (n = 304 cases; data not shown). When the analysis was restricted to all pneumonia cases in the placebo arm of the trial (n = 195 cases), the associations between the background characteristics and the risk of pneumonia were similar to all trial subjects, with the exception of the number of cigarettes smoked daily, which had no association with pneumonia in the placebo arm.

Dietary intakes of vitamin E and beta-carotene at baseline had no consistent association with the incidence of pneumonia in the placebo arm of the trial (Table 2). Supplementation with either vitamin E or beta-carotene had no overall impact on pneumonia incidence during the 5- to 8-year intervention period (Table 3), even when restricting the analysis to pneumonia cases with no concurrent diseases (n = 345; data not shown).

We analyzed whether age, smoking, body mass index, and consumption of coffee and alcohol modified the effect of vitamin E and beta-carotene

Table 1—*RR of Hospital-Treated Pneumonia by Baseline Characteristics, ATBC Study 1985–1993*

Characteristics	Subjects, No.	Pneumonia Cases, No.	Pneumonia Rate (1/1,000 Person-Years)	RR (95% CI)*	p Value for Trend
All subjects	29,133	898	5.3		
Age, yr					
50–54	10,342	183	3.0	1.00 reference	
55–59	9,367	265	4.9	1.38 (1.12–1.72)	
60–64	6,439	257	7.1	1.63 (1.27–2.11)	
65–69	2,985	193	12.0	2.41 1.78–3.27)	< 0.001
Body mass index†					
< 20	923	77	15.0	2.06 (1.56–2.74)	
20–24	10,366	330	5.5	1.00 reference	
25–29	13,372	378	4.9	0.96 (0.82–1.12)	
≥ 30	4,453	111	4.4	0.89 (0.71–1.11)	0.008
Cigarettes, per d					
5–19	10,559	320	5.3	1.00 reference	
20–29	13,378	419	5.4	1.16 (0.99–1.36)	
≥ 30	5,196	159	5.3	1.25 (1.01–1.55)	0.015
Duration of regular smoking, yr†					
< 32	7,687	138	3.0	1.00 reference	
32–42	14,976	408	4.7	1.20 (0.96–1.51)	
≥ 43	6,408	349	10.0	1.58 (1.19–2.10)	0.014
Age of smoking initiation, yr†					
≤ 20	21,657	701	5.6	1.00 reference	
≥ 21	7,469	196	4.5	0.89 (0.73–1.08)	0.6
Alcohol intake, g/d†					
0	3,029	119	6.9	1.26 (1.03–1.55)	
> 0–29	18,790	519	4.8	1.00 reference	
30–59	4,021	119	5.1	1.12 (0.91–1.38)	
≥ 60	1,271	51	7.0	1.39 (1.03–1.88)	0.004‡
Coffee intake, mL/d†					
< 300	4,028	172	7.5	1.00 reference	
300–599	9,824	297	5.2	0.74 (0.61–0.89)	
≥ 600	13,259	339	4.4	0.65 (0.53–0.78)	< 0.001
Education, yr					
Elementary school or less	23,004	734	5.6	1.00 reference	0.3
More than elementary school	6,129	164	4.5	0.90 (0.75–1.08)	
Marital status					
Married	23,367	688	5.1	1.00 reference	0.2
Not married	5,766	210	6.5	1.13 (0.95–1.34)	
Residential area†					
City (> 50,000 inhabitants)	12,346	411	5.5	1.00 reference	0.4
Small neighborhood	16,781	486	5.2	1.06 (0.92–1.23)	
Employment†					
Yes	16,804	349	3.5	1.00 reference	< 0.001
No	12,321	548	8.0	1.50 (1.27–1.78)	

*Proportional hazards regression model; for each variable, adjustment by all other categorized variables. The multivariate model is based on 801 pneumonia cases in 27,018 subjects with no missing data.

†Subjects with missing data on alcohol and coffee consumption (n = 2,022), body mass index (n = 19), age of smoking initiation (n = 7), duration of smoking (n = 62), residential area (n = 6), or employment (n = 8) were excluded in the respective univariate analyses.

‡Alcohol abstainers were excluded from trend analysis.

supplementation (Table 3). Only the age of smoking initiation was a significant modifying factor for both vitamin E and beta-carotene supplementation. The effect of vitamin E on the pneumonia risk was similar in subjects who had initiated smoking at 21 to 24 years of age (RR, 0.69; 95% CI, 0.47 to 1.00; n = 112 pneumonia cases), and in those who had initiated smoking at ≥ 25 years of age (RR, 0.61; 95% CI, 0.39 to 0.94; n = 84). Vitamin E had no effect on subjects who had initiated smoking at ≤ 15 years of age (RR, 1.05; 95% CI, 0.78 to 1.41; n = 180) or at 16 to 20 years of age (RR, 1.17; 95% CI, 0.98 to 1.39; n = 522). Moreover, the interaction between vitamin E supplementation and the continuous variable age of smoking initiation was highly significant (χ^2 [1 degree of freedom] = 8.8, p = 0.003). Dietary vitamin E did not modify the effect of vitamin E supplementation (Table 3).

Table 2—*RR of Hospital-Treated Pneumonia by Dietary Vitamin E and Beta-Carotene Intake, ATBC Study 1985–1993, the Placebo Arm*

Quartile of Intake*	Dietary Vitamin E				Dietary Beta-Carotene			
	Median Intake, mg/d	Pneumonia Cases, No.	Pneumonia Rate (1/1,000 Person-Years)	RR (95% CI)†	Median Intake, mg/d	Pneumonia Cases, No.	Pneumonia Rate (1/1,000 Person-Years)	RR (95% CI)†
1 (low)	6.7	59	6.1	1.00 (reference)	0.8	46	4.7	1.00 (reference)
2	9.3	47	4.7	0.89 (0.60–1.32)	1.4	65	6.6	1.51 (1.03–2.22)
3	12.2	48	4.9	1.02 (0.69–1.50)	2.2	45	4.5	1.07 (0.71–1.63)
4 (high)	18.2	42	4.2	0.92 (0.61–1.38)	3.7	40	4.0	0.96 (0.62–1.48)
p Value for trend				0.9				0.9

*Dietary intake at baseline.

†Proportional hazards regression model adjusted by age, number of cigarettes smoked, duration of regular smoking, and intake of coffee as continuous variables, and body mass index, alcohol consumption, and employment status as categorized in Table 1. Subjects with missing data on diet (n = 470), duration of smoking (n = 10), body mass index (n = 4), or employment status (n = 2) were excluded, thus leaving 6,802 subjects.

Beta-carotene supplementation increased the risk of pneumonia in subjects who initiated smoking at a later age, but had no effect on subjects who initiated smoking early (Table 3). The interaction between beta-carotene supplementation and the continuous variable age of smoking initiation was highly significant (χ^2 [1 degree of freedom]) = 8.4, p = 0.004). Dietary beta-carotene did not modify the effect of beta-carotene supplementation (Table 3).

Further exploratory subgroup analyses of supplementary vitamin E effects were carried out among subjects who initiated smoking at a later age to find out whether other factors might modify the vitamin E effect within this subgroup (Table 4). Only consumption of coffee was a significant effect modifier, so that vitamin E had a stronger protective effect in subjects who consumed more coffee. Also, smoking less than a pack of cigarettes per day was associated with a greater effect of vitamin E on the pneumonia risk, but this modification was only marginally significant. This finding has to be interpreted cautiously since it is influenced by the paradoxical rates among the placebo-treated subjects who initiated smoking at a later age; the incidence of pneumonia was 6.9 cases/1,000 person-years (based on 32 cases) among subjects who smoked less than a pack of cigarettes per day, whereas it was only 2.6 cases/1,000 person-years (based on 16 cases) among those who smoked a pack or more per day. Dietary vitamin E or C did not modify the effect of vitamin E supplementation in subjects who initiated smoking at later ages (Table 4).

Among the subjects who initiated smoking at a later age, the effect modification of current smoking on supplementary vitamin E effect was explored by using the smoking history reported by the cases at the follow-up visit 0 to 4 months before contracting pneumonia (Table 5). Vitamin E affected only weakly the risk of pneumonia in subjects who smoked continuously, whereas it decreased significantly the risk of pneumonia in subjects who quit smoking before contracting pneumonia. The median duration of smoking cessation was 1.7 years in the 23 subjects who had quit smoking before the occurrence of pneumonia. The estimate for subjects who quit smoking before the occurrence of pneumonia was not affected by adjustment for age, body mass index, coffee and alcohol consumption, and employment status (OR, 0.17; 95% CI, 0.05 to 0.59; n = 20 pneumonia cases with no missing data).

Discussion

We found no overall effect of supplementation with vitamin E or beta-carotene on the incidence of hospital-treated pneumonia in a large, placebo-controlled trial. Dietary intakes of vitamin E and beta-carotene were also not related to the risk of pneumonia. Nevertheless, among subjects who initiated smoking at a later age, vitamin E supplementation was associated with a reduced risk of pneumonia, whereas beta-carotene supplementation was associated with an increased risk.

In our study, pneumonia outcome was based on data from the National Hospital Discharge Register, and in general reflected clinically more severe cases of greater health and economic significance, with less severe cases of pneumonia treated as outpatients not being identified. Because almost all ATBC study participants lived at home, the pneumonia cases ascertained represent community-acquired disease, and medical records were not reviewed to rule out the relatively few nosocomial infections.

The overall incidence of pneumonia in our study population was 5.3 per 1,000 person-years, and the

Table 3—*RR of Hospital-Treated Pneumonia by Vitamin E and Beta-Carotene Supplementation, ATBC Study 1985–1993*

		Vitamin E		No Vitamin E				Beta-Carotene		No Beta-Carotene			
Subgroups	Subjects, No.	Cases, No.	Rate (1/1,000 Persons-Years)	Cases, No.	Rate (1/1,000 Person-Years)	RR (95% CI)*	Test for Interaction p Value	Cases, No.	Rate, (1/1,000 Person-Years)	Cases, No.	Rate (1/1,000 Person-Years)	RR (95% CI)	
All subjects	29,133	449	5.35	449	5.34	1.00 (0.88–1.14)		442	5.27	456	5.42	0.98 (0.85–1.11)	
Age at baseline, yr													
< 65	26,148	358	4.7	347	4.6	1.03 (0.89–1.19)	0.5	347	4.6	358	4.7	0.98 (0.84–1.13)	0.8
≥ 65	2,985	91	11.5	102	12.4	0.94 (0.70–1.24)		95	11.6	98	12.3	0.94 (0.70–1.24)	
Cigarettes, per day													
5–19	10,559	151	5.0	169	5.5	0.90 (0.72–1.12)	0.2	157	5.1	163	5.4	0.94 (0.75–1.17)	0.7
≥ 20	18,574	298	5.6	280	5.2	1.06 (0.90–1.25)		285	5.4	293	5.4	1.00 (0.84–1.17)	
Duration of regular smoking, yr†													
< 43	22,663	273	4.1	273	4.1	1.00 (0.85–1.19)	0.9	281	4.3	265	4.0	1.07 (0.90–1.27)	0.05
≥ 43	6,408	174	9.9	175	10.0	0.99 (0.80–1.22)		159	9.0	190	11.0	0.82 (0.66–1.01)	
Age of smoking initiation, yr†													
≤ 20	21,657	370	6.0	331	5.3	1.14 (0.98–1.32)	0.0007	328	5.3	373	6.0	0.88 (0.76–1.02)	0.004
≥ 21	7,469	79	3.6	117	5.5	0.65 (0.49–0.86)		114	5.3	82	3.8	1.42 (1.07–1.89)	
Coffee, mL/d†													
< 300	4,028	88	7.7	84	7.3	1.05 (0.78–1.42)	0.8	89	7.8	83	7.2	1.08 (0.80–1.46)	0.4
≥ 300	23,083	320	4.8	316	4.7	1.02 (0.87–1.19)		306	4.6	330	4.9	0.93 (0.80–1.09)	
Body mass index†													
< 25	11,289	208	6.4	199	6.1	1.04 (0.86–1.27)	0.6	191	5.9	216	6.6	0.90 (0.74–1.09)	0.3
≥ 25	17,825	240	4.7	249	4.9	0.97 (0.81–1.16)		250	4.9	239	4.7	1.04 (0.87–1.25)	
Dietary vitamin E, mg/d†													
< 10	11,759	208	6.2	214	6.3	0.99 (0.81–1.19)	0.6						
≥ 10	15,352	200	4.5	186	4.2	1.07 (0.87–1.31)							
Dietary β-carotene, mg/d†													
< 1.5	11,475							202	6.2	189	5.8	1.07 (0.88–1.31)	0.2
≥ 1.5	15,636							193	4.3	224	4.9	0.87 (0.72–1.06)	

*Proportional hazards regression model comparing participants who received vitamin E and those who did not, and participants who received beta-carotene and those who did not. No covariates were included in the model.

†Age of smoking initiation was missing for seven subjects. Duration of regular smoking was missing for 62 subjects. Body mass index was missing for 19 subjects. Coffee consumption and dietary vitamin E and beta-carotene was missing for 2,022 subjects.

Table 4—*RR of Hospital-Treated Pneumonia by Vitamin E Supplementation in Subjects Who Initiated Smoking at ≥ 21 Years, ATBC Study 1985–93*

Subgroups	Subjects, No.	Vitamin E		No Vitamin E		RR (95% CI)*	Test for Interaction p Value
		Cases, No.	Rate (1/1,000 Person-Years)	Cases, No.	Rate (1/1,000 Person-Years)		
All in the group	7,469	79	3.6	117	5.5	0.65 (0.49–0.86)	
Age at baseline, yr							
< 65	6,398	44	2.3	73	4.0	0.57 (0.39–0.83)	0.2
≥ 65	1,071	35	12.2	44	14.7	0.85 (0.54–1.32)	
Cigarettes, per d							
5–19	3,261	31	3.2	62	6.7	0.47 (0.30–0.73)	0.047
≥ 20	4,208	48	3.9	55	4.6	0.85 (0.57–1.25)	
Coffee, mL/d†							
< 300	1,115	19	5.7	14	4.5	1.21 (0.60–2.42)	0.022
≥ 300	5,795	49	2.9	92	5.6	0.51 (0.36–0.73)	
Body mass index†							
< 25	2,806	35	4.2	56	7.0	0.60 (0.39–0.91)	0.6
≥ 25	4,658	44	3.2	61	4.6	0.70 (0.47–1.03)	
Dietary vitamin E, mg/d†							
< 10	2,920	36	4.2	57	7.0	0.60 (0.39–0.91)	0.9
≥ 10	3,990	32	2.7	49	4.3	0.63 (0.40–0.98)	
Dietary vitamin C, mg/d†							
< 80	2,519	33	4.4	51	7.3	0.61 (0.39–0.94)	0.9
≥ 80	4,391	35	2.7	55	4.3	0.62 (0.40–0.94)	
Diagnosis‡							
Only pneumonia	7,469	30	1.4	51	2.4	0.57 (0.36–0.89)	
Pneumonia with concurrent diseases	7,469	49	2.2	66	3.1	0.71 (0.49–1.03)	

*Proportional hazards regression model comparing participants who received vitamin E and who did not. No covariates were included in the model.

†Body mass index was missing for 5 subjects; data on dietary vitamin E and C intake and coffee consumption were missing for 559 subjects.

‡Follow-up time includes all subjects. Depending on the kind of pneumonia, the case is listed in either of the two groups. Consequently, the rate for both kinds of diagnoses sum up to the total pneumonia rate.

age-specific rates of hospital-treated pneumonia we observed are similar to those across Finland.[26,27] A prospective study in eastern Finland searched for all pneumonia cases in the catchment population in the years from 1981 to 1982. The incidence rate of pneumonia in 45- to 59-year-old men was 9.8 per 1,000 person-years, and approximately half of these were treated at the hospital,[28] also leading to a rate estimate close to ours.

Table 5—*RR of Hospital-Treated Pneumonia by Vitamin E Supplementation in Subjects Who Initiated Smoking at ≥ 21 Years of Age, Role of Smoking Before the Occurrence of Pneumonia, ATBC Study 1985–1993*

Smoking Status*	Cases of Pneumonia, No.		OR (95% CI)†
	Vitamin E (n = 3,778)	No Vitamin E (n = 3,691)	
Smoked continuously	45	55	0.80 (0.53–1.19)
Quit smoking	4	19	0.21 (0.07–0.60)

*Smoking status reported at the latest follow-up visit before contracting pneumonia. Comparison of the continuous smokers to subjects who had quit smoking by the Fisher exact test yields p = 0.023 (two tailed), indicating that the distributions of pneumonia cases in these two groups are heterogeneous. A total of 73 pneumonia cases occurred among subjects who had dropped out of the trial before contracting pneumonia: 30 subjects in the vitamin E group and 43 subjects in the no-vitamin E group.

†Logistic regression model comparing vitamin E group to no-vitamin E group. No covariates were included in the model.

Risk factors for community-onset pneumonia have been characterized in several cohorts[28–32] and population-based case-control studies.[33–36] Pneumonia incidence increases progressively after the age of 50 years,[26–32,35,36] and leanness has been associated with increased risk.[29,31–33] Several studies[29,31,33–36] link cigarette smoking with higher pneumonia rates, with dose-response relations being reported between the number of cigarettes smoked daily and risk,[29,33–35] and life-time pack-years showing a similar trend.[33] The present study included only current smokers of at least five cigarettes daily (because of the primary intervention for lung cancer), and therefore estimating pneumonia risk relative to nonsmokers was not possible. Even among these smokers, however, men who smoked more cigarettes daily, and those who accumulated more years of smoking did have a higher incidence of pneumonia.

Abstainers and heavy users of alcohol had a slightly elevated risk of pneumonia compared with moderate alcohol consumers in our study. Alcoholics were

excluded from the ATBC study, which reduces our power to estimate the role of heavy drinking. Hospital-based case-control studies[37,38] and one cohort study[30] link alcoholism with a higher risk of pneumonia, but whether this results from the alcohol ingestion *per se*, or from other associated lifestyle factors remains unresolved. Other studies show no relationship between ordinary daily alcohol consumption and pneumonia risk,[29,31,33,36] but the number of pneumonia cases in these studies is small leading to low statistical power to detect small effects in the upper region of alcohol intakes.

We also observed reduced risk of pneumonia among heavy consumers of coffee, a finding consistent with our report of an inverse association between coffee consumption and the incidence of common cold episodes.[18] The caffeine in coffee is a close structural analog of theophylline, a bronchodilator, and caffeine has shown effects on pulmonary function.[39] Thus, high consumption of coffee may improve the ventilation of the bronchi and thus reduce the risk of getting pneumonia. Consumption of decaffeinated coffee is rare in Finland.

In subgroup analyses, vitamin E supplementation appeared to reduce by 35%, and beta-carotene supplementation to increase by 42% the risk of pneumonia among subjects who had initiated smoking at ≥21 years of age. There is no readily available biological mechanism to explain these effects in subjects initiating smoking in later age. The role of age of smoking initiation was analyzed as one indicator of smoking background, based on that smoking is an important risk factor of many pulmonary diseases. Longitudinal studies[40–43] have found that smoking in adolescence is associated with retarded growth of lung function, and a lower level of maximally attained lung function. In these studies,[40–43] the growth rate of lung function was slowed greatly if smoking was started by the age of 20 years. Thus, initiating to smoke in adolescence may have different effects on the risk of pulmonary diseases such as pneumonia in later life, than initiating to smoke in adulthood. We found, however, no direct association between the age of smoking initiation and the risk of hospital-treated pneumonia (Table 1).

The divergence in the effects of vitamin E in subgroups within a single trial is interesting as regards the substantial divergences in findings in the trials on vitamin C and respiratory infections.[44] Water-soluble antioxidant vitamin C regenerates lipid-soluble antioxidant vitamin E *in vitro*, and these two antioxidants appear to act synergistically in biological systems,[45–47] with both affecting the immune system[5,17,44]; therefore, these two antioxidants are of parallel interest. The effect of vitamin E supplementation on subjects who initiated smoking at later ages was, however, not modified by dietary vitamin E or C intake.

In conclusion, vitamin E and beta-carotene supplementation had no overall impact on the incidence of pneumonia in older male smokers. The observed effects among smoking subgroups should be considered cautiously, but may warrant further investigation of the role of vitamin E in populations with high risk of community-acquired pneumonia.

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