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Original investigation

β-Carotene Supplementation and Lung Cancer Incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study: The Role of Tar and Nicotine

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Abstract

Introduction: The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study demonstrated that β-carotene supplementation increases lung cancer incidence in smokers. Further, cigarettes with higher tar and nicotine content are associated with a higher risk of lung cancer. However, no studies have examined whether the increased risk associated with β-carotene supplementation in smokers varies by the tar or nicotine content of cigarettes.

Methods: The ATBC Study was a randomized, double-blind intervention trial conducted in southwest Finland. A total of 29 133 male smokers, aged 50–69 years, were enrolled and randomly assigned to one of four groups (α-tocopherol, β-carotene, both, or placebo). Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) of lung cancer risk by β-carotene trial assignment stratified by a priori categories of cigarette tar and nicotine content.

Results: The β-carotene supplementation group had significantly higher risk of developing lung cancer in all categories of tar content (yes vs. no β-carotene supplementation—ultralight cigarettes [≤7 mg tar]: HR = 1.31, 95% CI = 0.91 to 1.89; nonfiltered cigarettes [≥21 mg tar]: HR = 1.22, 95% CI = 0.91 to 1.64; *p* for interaction = .91). Similarly, there was no interaction with nicotine content (yes vs. no β-carotene supplementation—ventilated cigarettes [≤0.8 μg nicotine]: HR = 1.23, 95% CI = 0.98 to 1.54; nonfiltered cigarettes [≥1.3 μg nicotine]: HR = 1.22, 95% CI = 0.91 to 1.64; *p* for interaction = .83).

Conclusion: These findings support the conclusion that supplementation with β-carotene increases the risk of lung cancer in smokers regardless of the tar or nicotine content of cigarettes smoked. Our data suggest that all smokers should continue to avoid β-carotene supplementation.

Implications: Previous studies demonstrated that β-carotene supplementation increases risk of lung cancer in smokers. This study moves the field forward by examining the potential for modification of risk of lung cancer with different levels of tar and nicotine in cigarettes smoked, as interaction with carcinogens in these components of cigarette smoke is hypothesized to be the mechanism by which β-carotene increases risk. Our study provides evidence that the increased risk of lung cancer in smokers who take β-carotene supplements is not dependent upon the tar or nicotine level of cigarettes smoked and suggests that all smokers should continue to avoid β-carotene supplementation.

Introduction

Lung cancer is the most common cancer globally with 1.8 million new cases in 2012.[1] It is also the leading cause of death due to cancer, responsible for 1.59 million cancer deaths in 2012. The most important risk factor for the development of lung cancer is tobacco use, especially cigarette smoking.[2]

Early observational studies found a protective association between intake of vegetables rich in β-carotene and risk of lung cancer, which generated an interest in β-carotene supplementation as a potential chemoprevention strategy.[3,4] This led to the implementation of large cancer chemoprevention trials of β-carotene supplementation including the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study and the Beta-Carotene and Retinol Efficacy Trial (CARET). Despite the promising studies of dietary intake, these trials demonstrated that β-carotene supplementation causes lung cancer in people who smoke.[5–8] The ATBC Study reported an 18% excess in cumulative lung cancer incidence and an 8% excess in overall mortality in the β-carotene arm of the trial[6] whereas the CARET study showed 28% more lung cancer cases and 17% increase in the overall mortality in the active intervention group.[8]

There are many carcinogenic compounds in cigarette smoke that may cause lung cancer in smokers. After removal of nicotine and water, tar is the total particulate matter of cigarette smoke.[9] Most of the widely studied carcinogenic compounds from cigarettes are part of the "tar" of the cigarette. The relationship between cigarette tar content and lung cancer has been studied extensively.[10–14] Several studies found that the risk of lung cancer was higher in men and women smoking high-tar cigarettes, particularly nonfiltered cigarettes, when compared to medium-tar cigarettes (regular cigarettes), although the risk was not lower for individuals who smoked light or ultralight cigarettes.[10–14] Nicotine is the component of cigarette smoke primarily linked with addiction, but recent studies have demonstrated the involvement of nicotine in tumor promotion via various mechanisms.[15–18]

It is unknown whether the increased incidence of lung cancer among male smokers randomized to β-carotene supplementation[5–7] varied with tar and nicotine content of the cigarettes. Thus, we examined the interaction between β-carotene supplementation and the tar and nicotine content of cigarettes smoked and lung cancer incidence in the ATBC Study.

Methods

Study Design and Population

The ATBC Study was a joint project between the National Public Health Institute of Finland and the US National Cancer Institute. It was conducted between 1985 and 1993 in southwest Finland with the main objective of evaluating the effects of β-carotene and α-tocopherol supplementation on the incidence of lung and other cancers.[19]

Details of the trial design have been published previously.[19] Briefly, this was a randomized, double-blind, placebo-controlled chemoprevention trial. A total of 29 133 participants were included in the trial after applying the inclusion and exclusion criteria. Participants had to be men aged 50–69 years, smoking five or more cigarettes per day at the time of enrollment.[19] Participants were excluded from the trial if they previously had cancer or other serious illness at the time of enrollment. They were also excluded if they were using supplements containing vitamin E (>20 mg), vitamin A (>20.9 μmol), or β-carotene (>6 mg) at the time of enrollment.[19] Participants were randomly assigned to one of four treatment groups: α-tocopherol alone (dl-α-tocopherol acetate, 50 mg/d), β-carotene alone (20 mg/d), both α-tocopherol and β-carotene, or placebo, based on a 2 × 2 factorial design.[19] The trial was conducted for 5–8 years and ended in April 1993. We included data from the trial period and early postintervention, through 1996. Previous studies have shown that after this period, the effects of the β-carotene supplementation diminished.[20] We also conducted sensitivity analyses restricting the follow-up period to the end of trial, April 1993. The ATBC Study was approved by the institutional review board in the United States and Finland and written informed consent was obtained from all trial participants.[19]

Outcome Ascertainment

The follow-up of the participants for cancer outcomes continues through the Finnish Cancer Registry and the Register of Causes of Death. The Finnish Cancer registry was established in 1953 and has nearly 100% case ascertainment for cancer outcomes in the ATBC Study.[21] By the end of the trial (April 1993), 879 participants had been diagnosed with lung cancer whereas 1 393 lung cancer cases among the trial participants were diagnosed by 1996.

Exposure and Covariate Assessment

A detailed smoking history was included in the baseline questionnaire. Participants were asked whether they smoked manufactured or self-made cigarettes, and if the former, they were asked to identify the brand they mainly smoked from a list. Machine-measured tar and nicotine content of the cigarettes was assigned based on the brand reported by each participant. Self-made cigarettes were assumed to be unfiltered,[22,23] therefore participants who reported using self-made cigarettes (n = 2 794) were included in the highest category of tar and nicotine.

Statistical Analysis

Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) of lung cancer risk by β-carotene trial assignment, stratified by a priori categories of cigarette tar content (ultralight cigarettes ≤7 mg, light cigarettes 8–14 mg, medium/regular cigarettes 15–20 mg, high/nonfiltered/self-made cigarettes >20 mg) and nicotine content (ventilated filtered ≤0.8 μg, unventilated filtered >0.8 to ≤1.3 μg, nonfiltered >1.3 μg[12,24]). Statistical interaction was assessed using the likelihood ratio test. Apart from crude models, models were also adjusted for total cigarettes per day. Although this was a randomized controlled trial and confounding should be controlled for in the study design, adjustment for total cigarettes was included because the amount of tar and nicotine delivered to the body depends on the number of cigarettes smoked per day. Models stratified by tar were also further adjusted for nicotine content and vice versa. Cigarette tar and nicotine content was highly correlated (ρ before adding self-made cigarettes = 0.951, p value ≤.0001; ρ after adding self-made cigarettes = 0. 965, p value ≤.0001). All analyses were performed using SAS v.9.4 (SAS Institute Inc, Cary, NC).

Results

Characteristics of participants by β-carotene trial intervention and by a priori categories of tar and nicotine content are shown in Tables 1 and 2. Although many characteristics varied by tar and nicotine content, the patterns of the variations appeared to be similar within each

Table 1. Participant Characteristics (Medians) Stratified by Trial β-Carotene Supplementation and Tar Level of Cigarette Smoked

	No β-carotene				Yes β-carotene			
	Ultralight	Light	Regular	Nonfiltered	Ultralight	Light	Regular	Nonfiltered
	<7 mg	8–14 mg	15–20 mg	>20 mg	<7 mg	8–14 mg	15–20 mg	>20 mg
	(*n* = 1326)	(*n* = 2121)	(*n* = 9744)	(*n* = 1382)	(*n* = 1359)	(*n* = 2224)	(*n* = 9565)	(*n* = 1412)
Age at randomization (y)	57	56	56	57	57	57	57	57
Age at diagnosis (y)	71	72	71	70	71	71	71	70
BMI (kg/m^2)	26.0	26.1	26.0	25.6	26.1	26.0	26.0	29.0
Years smoked current cigarette	4	5	15	10	4	5	15	10
Years smoked regularly	36	35	36	39	36	35	36	40
Age when started to smoke (y)	20	20	19	18	20	20	19	18
Total number of cigarettes per day	20	20	20	20	20	20	20	20
Serum concentrations								
Baseline α-tocopherol (mg/L)	12.1	11.8	11.4	10.8	12.2	11.8	11.4	11.0
Baseline β-carotene (μg/L)	187	182	170	135	189	182	171	137
Follow up β-carotene (μg/L)	191	191	180	146	2968	3000	2968	2735
Total cholesterol (mmol/L)	6.1	6.2	6.2	6.0	6.2	6.2	6.2	6.0
Retinol (μg/L)	578	584	576	556	581	581	578	555
Dietary intake per day								
Alcohol (g)	10.7	10.5	11.0	13.4	10.3	10.3	11.1	13
Total Calories (kcal)	2491	2571	2624	2610	2521	2559	2618	2638
Dietary retinol (μg)	1190	1258	1268	1155	1201	1217	1265	1182
Dietary fatty acids (g)	90.1	93.8	98.0	94.8	90.3	95.0	97.7	98.0

BMI = body mass index.

Table 2. Participant Characteristics (Medians) Stratified by Trial β-Carotene Supplementation and Nicotine Level of Cigarette Smoked

	No β-carotene			Yes β-carotene		
	Ventilated filter	Unventilated filter	No filter	Ventilated filter	Unventilated filter	No filter
	≤0.8 μg	>0.8 to ≤1.3 μg	>1.3 μg	≤0.8 μg	>0.8 to ≤1.3 μg	>1.3 μg
	n = 3491	*n* = 9700	*n* = 1382	*n* = 3639	*n* = 9509	*n* = 1412
Age at randomization (y)	56	56	57	57	57	57
Age at diagnosis (y)	72	71	70	71	71	70
BMI (kg/m^2)	26.0	26.0	25.6	26.0	26.0	26.0
Years smoked current cigarette	5	15	10	5	15	10
Years smoked regularly	35	36	39	36	36	40
Age when started to smoke (y)	20	19	18	20	19	18
Total number of cigarettes per day	20	20	20	20	20	20
Serum concentrations						
Baseline α-tocopherol (mg/L)	11.9	11.4	10.8	12.0	11.4	11.0
Baseline β-carotene (μg/L)	185	170	135	185	171	137
Follow-up β-carotene (μg/L)	192	179	146	2991	2968	2735
Total cholesterol (mmol/L)	6.1	6.2	6.0	6.2	6.2	6.0
Retinol (μg/L)	581	576	556	582	578	555
Dietary intake per day						
Alcohol (g)	10.6	11.1	13.4	10.3	11.1	13
Total calories (kcal)	2527	2627	2610	2538	2620	2638
Dietary retinol (μg)	1219	1270	1155	1206	1267	1182
Dietary fatty acids (g)	92.3	98.0	94.8	93.1	97.7	98.0

BMI = body mass index.

β-carotene trial intervention group, as would be expected due to the randomized nature of the study.

We found that the previously reported increased risk of lung cancer with the trial β-carotene supplement was present in all categories of tar and nicotine content of the cigarettes smoked. For example, the hazard ratio for lung cancer comparing β-carotene supplementation to no β-carotene supplementation was similar in the two extreme categories of cigarette tar content: (β-carotene vs. no β-carotene—ultralight cigarettes: HR = 1.31, 95% CI = 0.91 to 1.89; nonfiltered cigarettes: HR = 1.22, 95% CI = 0.91 to 1.64; *p*

Table 3. Association Between Trial β-Carotene Supplementation and Risk of Lung Cancer, Stratified by Tar Level of Cigarette Smoked

Cigarette tar content	β-Carotene intervention group	No. of cases	No. of person-years	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Ultralight (<7 mg)	No	50	11 096	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Yes	67	11 336	1.31 (0.91 to 1.89)	1.31 (0.91 to 1.89)	1.38 (0.95 to 1.99)
Light (8–14 mg)	No	85	18 090	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Yes	103	18 642	1.18 (0.89 to 1.57)	1.17 (0.88 to 1.56)	1.17 (0.88 to 1.56)
Regular (15–20 mg)	No	430	81 027	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Yes	480	79 120	1.15 (1.01 to 1.31)	1.15 (1.01 to 1.31)	1.15 (1.01 to 1.31)
Nonfiltered (>20 mg)	No	80	10 936	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Yes	98	11 031	1.22 (0.91 to 1.64)	1.22 (0.91 to 1.64)	1.22 (0.91 to 1.64)
		p for interaction		*.91*	*.92*	*.83*

HR = hazard ratio; CI = confidence interval.

[a]Unadjusted model.

[b]Adjusted for total number of cigarettes per day.

[c]Adjusted for total number of cigarettes per day and nicotine content.

for interaction = .91) (Table 3). Adjustment for total cigarettes per day and nicotine content did not change the interaction between β-carotene and tar content (Table 3). Similarly, adjustment for age did not change the interaction between β-carotene and tar content (β-carotene vs. no β-carotene—ultralight cigarettes: age-adjusted HR = 1.26, 95% CI = 0.87 to 1.81; nonfiltered cigarettes: age-adjusted HR = 1.14, 95% CI = 0.85 to 1.53; *p* for interaction = .96).

The hazard ratio for lung cancer comparing β-carotene supplementation to no β-carotene supplementation was also similar for the two extreme categories of cigarette nicotine content (β-carotene vs. no β-carotene—ventilated cigarettes HR = 1.23, 95% CI = 0.98 to 1.54; nonfiltered cigarettes HR = 1.22, 95% CI = 0.91 to 1.64, *p* for interaction = .83) (Table 4). The association did not change meaningfully even after adjustment for total cigarettes and tar levels (Table 4). Similarly, adjustment for age did not change the interaction between β-carotene and cigarette nicotine content (β-carotene vs. no β-carotene—ventilated cigarettes: age-adjusted HR = 1.22, 95% CI = 0.97 to 1.53; nonfiltered cigarettes: age-adjusted HR = 1.14, 95% CI = 0.85 to 1.53; *p* for interaction = .87).

When we restricted our analysis to the 879 cases that occurred through the end of the trial period in April 1993, the results were unchanged (β-carotene vs. no β-carotene—ultralight cigarettes: HR = 1.24, 95% CI = 0.77 to 2.00; nonfiltered cigarettes: HR = 1.21, 95% CI = 0.84 to 1.76; *p* for interaction = .90; ventilated cigarettes: HR = 1.23, 95%CI = 0.92 to 1.65; nonfiltered cigarettes HR = 1.21, 95% CI = 0.84 to 1.76, *p* for interaction = .95). Higher dietary β-carotene in the non–β-carotene supplemented men was related to lower risk of lung cancer but did not ameliorate the higher risk in the β-carotene group (data not shown).

Discussion

In this analysis, we found that β-carotene supplementation caused lung cancer in male smokers regardless of the tar or nicotine content of the cigarettes smoked. Men smoking the lowest tar cigarettes had a 31% higher risk of lung cancer when supplemented with β-carotene whereas men smoking the highest tar cigarettes had a similar 22% higher risk. Likewise, men smoking the lowest nicotine cigarettes had a 23% higher risk of lung cancer when supplemented with β-carotene whereas men smoking the highest nicotine cigarettes had a 22% increased risk.

Although observational studies had reported a protective association with intake of foods high in β-carotene, randomized trials have demonstrated that β-carotene supplementation in the context of cigarette smoke exposure increases the risk of developing lung cancer.[5–8,25] In addition, several studies have also shown that risk of lung cancer rises with increasing cigarette tar content in both male and female smokers.[12,13] Tar is composed of carcinogenic compounds including benzopyrene, dibenzanthracene, and other polyaromatic hydrocarbons, which may cause formation of free-radical species.[26] Due to the presence of such carcinogens, it is plausible that tar is affecting the risk of lung cancer by multiple biological pathways and β-carotene may interact with it due to its antioxidant properties,[12] leading to DNA damage in the lung epithelial cells.[27] Mouse models of lung cancer have shown that nicotine may have a limited ability to initiate tumorigenesis, but it plays an important role in tumor promotion by inducing invasion and epithelial–mesenchymal transition.[17] The tumor-promoting role of nicotine has also been studied in cell lines, and it has been shown that nicotine may act on nicotine acetylcholine receptors to promote tumor growth.[16]

β-Carotene supplementation studies in a nonhuman model (ferrets) exposed to tobacco smoke have implicated the possibility of reduced retinoid signaling due to reduction of the RARβ gene expression and amplified expression of activator protein-1, leading to cancer formation.[28] Because interaction between carcinogens in tobacco smoke has been implicated as the biologic mechanism by which β-carotene supplementation causes lung cancer,[27] and because higher tar levels in cigarettes have been associated with an increased risk of lung cancer in some studies,[10–14] we had hypothesized that the β-carotene and lung cancer association might be stronger in men smoking higher tar cigarettes. Similarly, because of the promotional activity of nicotine on tumor cells,[15] we had hypothesized that nicotine levels could modify the association between lung cancer and β-carotene supplementation. However, we found no such difference by tar or nicotine content of cigarettes smoked, possibly indicating that some threshold(s) for smoking intensity or tar and nicotine content were reached by all participants based on the eligibility criterion of smoking at least five cigarettes daily. To the best of our knowledge, no previous studies have examined the interaction between cigarette tar and nicotine yield and β-carotene supplementation.

The randomized nature of this trial, large sample size, and the high-quality data on smoking behavior and cigarette tar and nicotine content are some of the strengths of this study.[5–7,19,29] Participants were supplemented with β-carotene for a long period (ie, 5–8 years), providing ample time to observe the effect of the supplement after

Table 4. Association Between Trial β-Carotene Supplementation and Risk of Lung Cancer, Stratified by Nicotine Level of Cigarette Smoked

Cigarette nicotine content	β-Carotene intervention group	No. of cases	No. of person-years	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[c]
Ventilated filtered (≤0.8 µg)	No	135	29 527	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Yes	171	30 474	1.23 (0.98 to 1.54)	1.22 (0.98 to 1.53)	1.24 (0.99 to 1.56)
Unventilated filtered (>0.8 to ≤1.3µg)	No	430	80 687	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Yes	479	78 625	1.15 (1.01 to 1.31)	1.15 (1.01 to 1.31)	1.15 (1.01 to 1.31)
Regular (>1.3 µg)	No	80	10 936	1.0 (ref)	1.0 (ref)	1.0 (ref)
	Yes	98	11 031	1.22 (0.91 to 1.64)	1.22 (0.91 to 1.64)	1.22 (0.91 to 1.64)
		p for interaction		*.91*	*.92*	*.83*

HR = hazard ratio; CI = confidence interval.

[a]Unadjusted model.

[b]Adjusted for total number of cigarettes per day.

[c]Adjusted for total number of cigarettes per day and tar content.

its stabilization in the body.[5,6] Because this study was conducted in male smokers from Finland, the results may not be generalizable to women or other ethnic groups. Cigarette brands may vary from one country to another; hence, results from this study may not apply to countries other than Finland. Further, only one dose and preparation of β-carotene was provided to the participants in this trial, so it is possible that our results are not generalizable to individuals supplemented with other dosages or preparations of β-carotene. It should be noted, however, that the CARET study found a similar increased risk of lung cancer among smokers supplemented with β-carotene[5–8,19,29]; this study was conducted in the United States and included men and women, as well as some nonwhite participants, and used a different dose and preparation of β-carotene.[8] This consistency suggests that lack of generalizability may not be a major issue. Another minor limitation of this study could be that the information on cigarette smoking and brand of cigarette smoked were self-reported and obtained only at baseline.[30] Various studies have shown that machine-measured tar and nicotine does not reflect the actual exposure to tar and nicotine. Individual variability in inhalation patterns among the participants could have contributed to differences in delivered tar and nicotine levels that would not be captured by knowing the brand of cigarette smoked. In addition, smokers smoking light or ventilated cigarettes have shown to compensate via deep inhalation, more puffs, or covering the vent holes while smoking.[31,32] Thus, the true delivered doses of tar and nicotine might be more similar across groups than our data on type of cigarette smoked would suggest, causing our similar findings across tar and nicotine categories.

In summary, these findings support the conclusion that supplementation with β-carotene increases the risk of lung cancer in smokers regardless of the tar or nicotine content of cigarettes smoked. Our data suggest that all smokers, regardless of the type of cigarette smoked, should continue to avoid β-carotene supplementation.

Declaration of Interests

None declared.

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