Risk Factors for Lung Cancer and for Intervention Effects in CARET, the Beta-Carotene and Retinol Efficacy Trial

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Background: Evidence has accumulated from observational studies that people eating more fruits and vegetables, which are rich in β-carotene (a violet to yellow plant pigment that acts as an antioxidant and can be converted to vitamin A by enzymes in the intestinal wall and liver) and retinol (an alcohol chemical form of vitamin A), and people having higher serum β-carotene concentrations had lower rates of lung cancer. The Beta-Carotene and Retinol Efficacy Trial (CARET) tested the combination of 30 mg β-carotene and 25 000 IU retinyl palmitate (vitamin A) taken daily against placebo in 18 314 men and women at high risk of developing lung cancer. The CARET intervention was stopped 21 months early because of clear evidence of no benefit and substantial evidence of possible harm; there were 28% more lung cancers and 17% more deaths in the active intervention group (active = the daily combination of 30 mg β-carotene and 25 000 IU retinyl palmitate). Promptly after the January 18, 1996, announcement that the CARET active intervention had been stopped, we published preliminary findings from CARET regarding cancer, heart disease, and total mortality. ***Purpose:*** We present for the first time results based on the pre-specified analytic method, details about risk factors for lung cancer, and analyses of subgroups and of factors that possibly influence response to the intervention. ***Methods:*** CARET was a randomized, double-blinded, placebo-controlled chemoprevention trial, initiated with a pilot phase and then expanded 10-fold at six study centers. Cigarette smoking history and status and alcohol intake were assessed through participant self-report. Serum was collected from the participants at base line and periodically after randomization and was analyzed for β-carotene concentration. An Endpoints Review Committee evaluated endpoint reports, including pathologic review of tissue specimens. The primary analysis is a stratified logrank test for intervention arm differences in lung cancer incidence, with weighting linearly to hypothesized full effect at 24 months after randomization. Relative risks (RRs) were estimated by use of Cox regression models; tests were performed for quantitative and qualitative interactions between the intervention and smoking status or alcohol intake. O'Brien–Fleming boundaries were used for stopping criteria at interim analyses. Statistical significance was set at the .05 α value, and all *P* values were derived from two-sided statistical tests. ***Results:*** According to CARET's pre-specified analysis, there was an RR of 1.36 (95% confidence interval [CI] = 1.07-1.73; *P* = .01) for weighted lung cancer incidence for the active intervention group compared with the placebo group, and RR = 1.59 (95% CI = 1.13-2.23; *P* = .01) for weighted lung cancer mortality. All subgroups, except former smokers, had a point estimate of RR of 1.10 or greater for lung cancer. There are suggestions of associations of the excess lung cancer incidence with the highest quartile of alcohol intake (RR = 1.99; 95% CI = 1.28-3.09; test for heterogeneity of RR among quartiles of alcohol intake has *P* = .01, unadjusted for multiple comparisons) and with large-cell histology (RR = 1.89; 95% CI = 1.09-3.26; test for heterogeneity among histologic categories has *P* = .35), but not with base-line serum β-carotene concentrations. ***Conclusions:*** CARET participants receiving the combination of β-carotene and vitamin A had no chemopreventive benefit and had excess lung cancer incidence and mortality. The results are highly consistent with those found for β-carotene in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study in 29 133 male smokers in Finland. ***Implications:*** Individuals at high risk of developing lung cancer, i.e., current smokers and asbestos-exposed workers, should be discouraged from taking supplemental β-carotene (and the combination of β-carotene with vitamin A). Safety and efficacy should be demonstrated before recommending use of vitamin supplements in any population. [J Natl Cancer Inst 1996;88:1550-9]

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See "Notes" section following "References."

Since the hypothesis of Peto et al. (*1*) in 1981 that β-carotene might reduce the incidence of cancer, especially lung cancer, evidence has accumulated from observational studies that people eating more fruits and vegetables, which are rich in β-carotene (a violet to yellow plant pigment that acts as an antioxidant and can be converted to vitamin A by enzymes in the intestinal wall and liver) and retinol (an alcohol chemical form of vitamin A), and people having higher serum β-carotene concentrations had lower rates of lung cancer (*2,3*). Of the diverse components of fruits and vegetables, β-carotene was considered the best candidate for a chemopreventive effect; its antioxidant activity provided a plausible mechanism. Epidemiologic studies, strongly buttressed by chemoprevention bioassays using potent carcinogens in animals, made vitamin A and its analogues excellent candidates for chemoprevention in humans. In 1983, the National Cancer Institute approved our proposal to initiate pilot studies of the safety and feasibility of a chemoprevention trial of β-carotene and retinol in smokers and in asbestos-exposed workers at high risk for lung cancer. After the pilot studies showed successful recruitment, negligible toxicity, and excellent adherence (*4,5*), a 10 times larger recruitment for testing efficacy was launched in 1988 (*6,7*); stepwise recruitment was completed in September 1994. Thus, the Beta-Carotene and Retinol Efficacy Trial (CARET) tested the combination of 30 mg β-carotene and 25 000 IU vitamin A against placebo in 18 314 men and women at high risk for lung cancer.

The CARET active intervention was stopped 21 months early because of clear evidence of no benefit and substantial evidence of possible harm; there were 28% more lung cancers and 17% more deaths in the active intervention group (*8*). Promptly after the January 18, 1996, announcement that the CARET active intervention had been stopped, we published preliminary findings from CARET regarding cancer, heart disease, and total mortality (*8*). In this article, we present for the first time results based on the pre-specified analytic method, details about risk factors for lung cancer, and analyses of subgroups and of factors that possibly influence response to the intervention.

Subjects and Methods

Background and Base Line

The strategy, design, methods, eligibility criteria, pilot study findings, recruitment success, safety monitoring, end-points ascertainment and review process, and preliminary findings have been published (*4-8*). Briefly, CARET pilot studies investigated 816 men with substantial occupational exposures to asbestos who received the combination of 15 mg β-carotene and 25 000 IU retinol daily or placebo (1:1) and 1029 men and women with extensive cigarette smoking histories who received 30 mg β-carotene, 25 000 IU retinol, both, or neither (2 × 2 factorial design; hence, three fourths of patients received one or both active agents, and one fourth received placebo only). In 1988, all pilot study participants in active groups were converted to the CARET efficacy regimen of 30 mg β-carotene plus 25 000 IU retinyl palmitate taken daily, and the project was expanded 10-fold at six study centers around the country during the next 3 years (additional randomization 1:1 active/placebo). The synthetic β-carotene, retinol (pilot studies), and retinyl palmitate (CARET) were manufactured by Hoffmann-La Roche, Inc., Nutley, NJ. The continuing pilot study participants are called the pilot cohort, whereas the participants recruited later are designated as the efficacy cohort. The design (*6*) projected active intervention until late 1997, encompassing 110 000 person-years of follow-up from time of randomization for the 18 314 total participants recruited. A 2 × 2 factorial design for the efficacy trial was rejected because animal studies (*9*) showed that administration of retinol or retinyl palmitate markedly suppressed the conversion of β-carotene to vitamin A, so their effects could not be considered independent. Written informed consent was obtained from all participants prior to their entry into the trial and prior to initiation of ancillary studies and protocol modifications (dosage consolidation in 1988; collection of blood for DNA analysis in 1994) during the trial. CARET activities were reviewed and approved annually by the institutional review boards at the six CARET centers.

Base-line characteristics of the CARET participants were well balanced between intervention groups (*8*). The 14 254 smokers (44% women) had a mean age of 58 years and a mean of 49 pack-years of cigarette smoking; 66% were current smokers upon recruitment (means of 24 cigarettes/day and 48 pack-years), and 34% were former smokers (means of 3 years since quitting after smoking 28 cigarettes/day and 52 pack-years). The 4060 asbestos-exposed male workers had a mean age of 57 years; 3% were never smokers (from the pilot study), 58% were former smokers, and 38% were current smokers, with a mean of 43 pack-years of smoking history (40 pack-years for former smokers and 47 pack-years for current smokers) and a mean of 10 years since quitting among the former smokers. They had means of 35 years since first asbestos exposure and 27 years' duration of asbestos exposure on the job; approximately two thirds had chest x rays positive for asbestos-related disease. All smokers were encouraged and were given assistance, if willing, to quit smoking, and all former smokers were encouraged to sustain that status. A net smoking cessation rate of 5% per year was achieved.

Data Collection and Follow-up

Data from participant self-reports were collected routinely about food frequency (including alcohol intake), cigarette smoking, and medical diagnoses; blood specimens were obtained from all participants and were analyzed routinely for all pilot participants and a 10% sample of efficacy participants (*4-7*). CARET participants were considered to be continuous smokers if they reported smoking at every contact when smoking was assessed and continuous former smokers if they were former smokers at treatment randomization and reported not smoking at every contact at which smoking was assessed. More than 80% of participants were classified as continuous smokers or continuous former smokers; the remainder included participants who quit smoking or resumed smoking and 132 participants from the asbestos pilot study who were never smokers. Because distribution of reported alcohol intake was markedly different between males and females, we analyzed the effects of alcohol consumption and interaction of alcohol intake with other lung cancer risk factors and the intervention assignment using quartiles and tertiles and sex-specific quartiles from CARET, as well as cut points from the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) quartiles of intake (*10*).

Case Ascertainment and Review

Through December 15, 1995, CARET received reports of 2420 end points, including 1446 cancers (in 1353 participants) and 974 deaths, with a median of 3.7 years and mean of 4.0 years of follow-up after randomization for all CARET participants. We excluded 746 additional cancer reports that were not CARET end points: 500 basal cell and squamous cell skin cancers, eight cancers diagnosed prior to randomization, and 238 recurrences, metastatic presentations, or noncancers. For each reported end point, clinical records were obtained for confirmation by the CARET Endpoints Review Committee. As part of this review, pathology or cytology specimens were obtained for tumors involving the lung for independent review by the CARET pathologist (S. Hammar) to confirm origin, location, and histology. Of the incident primary lung cancers among 388 participants reported through December 15, 1995, 316 had been reviewed by the CARET pathologist (80% histology, 20% cytology), seven were diagnosed clinically, and 65 were still in the data collection and review process. The process also involved independent assessment by two physicians and further committee review to resolve disagreements. Cases were coded according to the International Classification of Diseases for Oncology (*11*). Cases were termed closed when they completed the entire review process.

Histologic, immunohistochemical, and ultrastructural criteria were used to diagnose non-small-cell and small-cell lung neoplasms (*12-14*). Neoplasms composed of cells that would put them into a non-small-cell category were classified as large-cell undifferentiated carcinomas if they did not show definite features of adenocarcinoma, squamous cell carcinoma, or neuroendocrine carcinoma. Small-cell undifferentiated carcinoma can be seen in association with adenocar-

cinoma or squamous cell carcinoma (combined neoplasms) or with neoplastic large cells (mixed small-cell and large-cell carcinomas). Neuroendocrine carcinomas, which are infrequent, may be misdiagnosed as adenocarcinoma, squamous cell carcinoma, or large-cell undifferentiated carcinoma; if any question existed concerning whether a lung neoplasm was a non-small-cell neuroendocrine carcinoma, immunohistochemical and/or ultrastructural studies of neuroendocrine markers were performed (*14*). These criteria for the classification of lung neoplasms were applied to all cases as strictly as possible and blinded to intervention assignment.

In general, there is approximately a 70% accuracy in prediction of cell type from cytologic specimens, ranging from 90% for small-cell carcinoma to 40% for large-cell undifferentiated carcinoma, with the use of precise criteria described elsewhere (*13*). Cytologically malignant cells in a specimen that did not show specific features of squamous cell carcinoma, adenocarcinoma, or small-cell carcinoma were classified as large-cell undifferentiated carcinomas.

Statistical Analysis

The primary analysis, based on intention to treat, was designed to test for differences between intervention groups in the incidence of lung cancer by use of a stratified, weighted logrank statistic (*6,15*), with the weight function rising linearly from 0 at the time of randomization to 1.0 at 2 years after randomization and thereafter. This function is the optimal weighting for the logrank statistic if the incidence of lung cancer is proportional to the mean vitamin intake over the previous 2 years. Based on a two-sided test for the primary analysis, CARET had 80% power if carried to completion to detect a 22% observed reduction or 24% observed increase in lung cancer incidence. Since the logrank test does not provide a relative risk (RR) estimate, we estimated RRs with confidence intervals (CIs) by Cox regression models (*15*). Analyses presented here include P values of unweighted, stratified logrank tests and RR estimates from unweighted and weighted Cox proportional hazards models. We fit Cox regression models with time-dependent covariates, which adjust for a time lag to full intervention effect (postulated in the primary analysis to be at 2 years after randomization) and for the change in vitamin dosages between the 1985-1988 pilot period and the post-1988 standard dosage (*6,7*). Specifically, the predictor variable for an individual at time t was the average dose of β-carotene prescribed by the trial for that individual over the 2-year period preceding time t. Individuals in the placebo group had a predictor variable of 0 at all times, whereas individuals recruited in the efficacy cohort in the active vitamin group had a predictor variable that rose from 0 at randomization to 1.0 at 2 years after randomization. The predictor variable in pilot participants receiving active vitamins was more complex because of the vitamin dosage change at transition, but it followed the same definition. We explored the sensitivity of our conclusions to our choice of weight function by computing P values and RR estimates for a range of durations of the weighted period. By including the appropriate interaction terms in the Cox models, we tested associations between the intervention and smoking status or alcohol use for quantitative interactions (i.e., that different subgroups have different risks) and for qualitative (crossover) interactions (i.e., that different subgroups have opposite directions of risk) (*16*). We evaluated the heterogeneity of RR among different levels of alcohol consumption by using likelihood ratio tests (*15*) between Cox models, including and excluding indicator variables for the levels of the predictor. We evaluated the heterogeneity of risk among different histologies of lung cancer by the likelihood ratio test (*17*) for independence in the table of number of cancers per intervention group by histologic type. The formal CARET monitoring policy for stopping the trial early as a result of efficacy or adverse effect of the study vitamins was based on O'Brien–Fleming boundaries (*18*) applied to the weighted number of confirmed (closed) lung cancer end points; the critical P values were .0006 for the first interim analysis in 1994 and .007 for the second interim analysis in 1995.

Results

Lung Cancer Incidence

Lung cancer incidence is the primary end point for CARET. Through December 15, 1995, 388 participants (of whom 254 had died) were reported to have first occurrence of lung cancer. The review of end points was complete for 286; 90% of CARET cases initially reported as lung cancer have been confirmed as incident primary lung cancers when closed by the Endpoints Review Committee. Five participants had two primary lung cancers each. The crude incidence rates for the pilot and efficacy cohorts, for both asbestos-exposed and smoker populations, are given in Table 1 by intervention group. The rates were quite similar in the two populations, reflecting less current smoking in the asbestos-exposed population. Overall, the incidence of lung cancer was 5.9 per 1000 persons per year in the active intervention group versus 4.6 in the placebo group.

This difference (Table 2) corresponded to an estimated unweighted RR of 1.28 (95% CI = 1.04-1.57; P = .02) and an estimated weighted RR of 1.36 (95% CI = 1.07-1.73; P = .01). The stratified logrank test with weighting of end points for the first 2 years, when applied to the 286 closed lung cancer cases,

Table 1. Numbers of participants randomly assigned to treatment groups, numbers of lung cancers and person-years of follow-up, crude lung cancer incidence rates (×1000), and 95% confidence intervals by population, cohort, and intervention group (closed plus open cases)

	Asbestos-exposed participants		Heavy smokers		Total†	
	Active*	Placebo	Active*	Placebo	Active*	Placebo
Pilot cohort						
No. randomly assigned	420	396	773	256	1193	652
Lung cancers/person-years of follow-up	17/3349	15/3227	43/6395	7/2093	60/9745	22/5320
Lung cancer incidence rate, ×1000	5.1	4.6	6.7	3.4	6.2	4.1
(95% confidence interval)	(3.2-8.2)	(2.8-7.7)	(5.0-9.1)	(1.6-7.0)	(4.8-7.9)	(2.7-6.3)
Efficacy cohort						
No. randomly assigned	1624	1620	6603	6622	8227	8242
Lung cancers/person-years of follow-up	45/6899	29/6938	124/22 040	108/22 193	169/28 939	137/29 131
Lung cancer incidence rate, ×1000	6.5	4.2	5.6	4.9	5.8	4.7
(95% confidence interval)	(4.9-8.7)	(2.9-6.0)	(4.7-6.7)	(4.0-5.9)	(5.0-6.8)	(4.0-5.6)
Total†						
No. randomly assigned	2044	2016	7376	6878	9420	8894
Lung cancers/person-years of follow-up	62/10 249	44/10 165	167/28 435	115/24 285	229/38 684	159/34 450
Lung cancer incidence rate, ×1000	6.1	4.3	5.9	4.7	5.9	4.6
(95% confidence interval)	(4.7-7.8)	(3.2-5.8)	(5.0-6.8)	(3.9-5.7)	(5.2-6.7)	(4.0-5.4)

*Active = the daily combination of 30 mg β-carotene and 25 000 IU retinyl palmitate.

†Totals of person-years may differ from the sum of the elements in the table because of rounding error.

Table 2. Lung cancer incidence: number of events, logrank *P* values, estimated relative risks, and 95% confidence intervals with or without downweighting

	Events*/No. randomly assigned		Unweighted analysis			Weighted analysis		
	Active†	Placebo	Relative risk‡	95% confidence interval§	*P*‖	Relative risk‡	95% confidence interval§	*P*‖
All participants	229/9420	159/8894	1.28	1.04-1.57	.02	1.36	1.07-1.73	.01
Asbestos-exposed participants	62/2044	44/2016	1.40	0.95-2.07	.08	1.82	1.16-2.84	.008
Heavy smokers	167/7376	115/6878	1.23	0.96-1.56	.09	1.20	0.90-1.60	.21
Males	100/4168	64/3797	1.25	0.91-1.73	.17	1.23	0.85-1.78	.28
Females	67/3208	51/3081	1.19	0.82-1.72	.36	1.13	0.71-1.79	.27
Pilot cohort	60/1193	22/652	1.45	0.88-2.40	.14	1.56	0.92-2.64	.09
Asbestos-exposed	17/420	15/396	1.10	0.55-2.20	.79	1.25	0.56-2.82	.58
Smokers	43/773	7/256	2.01	0.90-4.47	.08	1.83	0.90-3.74	.08
Efficacy cohort	169/8227	137/8242	1.24	0.99-1.56	.06	1.31	0.99-1.72	.05
Asbestos-exposed	45/1624	29/1620	1.57	0.98-2.50	.06	2.13	1.23-3.69	.005
Smokers	124/6603	108/6622	1.16	0.89-1.50	.27	1.09	0.79-1.50	.58
Current smokers at base line	168/5684	105/5324	1.40	1.10-1.80	.007	1.40	1.04-1.86	.02
Heavy smokers	136/4903	81/4547	1.42	1.07-1.87	.01	1.37	0.98-1.91	.06
Asbestos-exposed	32/781	24/777	1.35	0.80-2.30	.26	1.49	0.82-2.70	.19
Former smokers at base line	61/3668	54/3506	1.04	0.72-1.51	.82	1.29	0.83-2.01	.25
Heavy smokers	31/2473	34/2331	0.80	0.48-1.31	.37	0.80	0.44-1.45	.46
Asbestos-exposed	30/1195	20/1175	1.47	0.83-2.59	.18	2.34	1.17-4.68	.01
Continuous smokers	109/4184	64/4024	1.52	1.12-2.08	.007	1.59	1.09-2.31	.02
Heavy smokers	88/3656	52/3512	1.48	1.05-2.10	.02	1.44	0.95-2.19	.08
Asbestos-exposed	21/528	12/512	1.70	0.84-3.45	.14	2.33	0.98-5.51	.05
Continuous former smokers	54/3344	47/3187	1.05	0.70-1.55	.83	1.28	0.79-2.05	.31
Heavy smokers	28/2218	30/2086	0.80	0.47-1.35	.40	0.77	0.41-1.46	.43
Asbestos-exposed	26/1126	17/1101	1.49	0.81-2.74	.20	2.43	1.14-5.21	.02

*Closed plus open lung cancer cases (n = 388).
†Active = the daily combination of 30 mg β-carotene and 25 000 IU retinyl palmitate.
‡Estimated relative risk of active to placebo stratified on high-risk population, cohort, and study center, for the logrank test (unweighted analysis) and for the Cox regression model with time-dependent covariate (weighted analysis; *see* "Subjects and Methods" section).
§95% confidence interval for the estimated relative risk of active to placebo.
‖Two-sided.

had a chi-squared value of 4.62 with 1 degree of freedom, corresponding to $P = .03$.

Table 2 presents the RR estimates from the Cox regression models with time-dependent covariates to match the weighted logrank statistic, together with the unweighted results published in part previously (*8*). The findings were remarkably consistent, with an excess of lung cancers in all subgroups in the top half of the table. The 95% lower CI limit exceeded 1.0 for the total CARET population (both unweighted and weighted analyses) and also for the asbestos-exposed subpopulation in the weighted analysis (Table 2). Compared with the unweighted analysis, the weighted analysis indicated higher RRs for the total population and for the asbestos-exposed population, with somewhat lower, still elevated RRs for the smokers. The point estimate of the RR in the weighted analysis of the whole CARET population was the same for closed and for closed plus pending lung cancer cases (RRs = 1.36).

To evaluate the time course of appearance of lung cancers, we tested the sensitivity of the weighting function to the duration of the weighted period and plotted cumulative incidence. Table 3 shows the RR and *P* values for lung cancer incidence for the total CARET population with linear weighting to year *N* and with truncation to remove cases occurring before year *N*. In the overall CARET population, the cumulative lung cancer incidence curves started to separate at 18 months after randomization (*8*). Cumulative incidence plots for each of the four population/cohort subgroups (Fig. 1) were monitored by the Safety and

Table 3. *P* values, estimated relative risks, and 95% confidence intervals for weighted and truncated analyses of lung cancer incidence by duration of downweighted/truncated period

	Weighted analysis			Truncated analysis		
Downweighted/ truncated period, y	Relative risk*	95% confidence interval†	*P*‡	Relative risk*	95% confidence interval†	*P*‡
0	1.28	1.04-1.57	.02	1.28	1.04-1.57	.02
1	1.31	1.06-1.63	.01	1.28	1.02-1.61	.03
2	1.36	1.07-1.73	.01	1.24	0.95-1.63	.12
3	1.39	1.06-1.83	.02	1.44	1.02-2.02	.04
4	1.45	1.06-1.97	.02	1.62	1.05-2.50	.03
5	1.53	1.08-2.17	.02	1.26	0.71-2.26	.43

*Estimated relative risk of active (i.e., the daily combination of 30 mg β-carotene and 25 000 IU retinyl palmitate) to placebo stratified on high-risk population, cohort, and study center, for the Cox regression model with time-dependent covariate (weighted analysis; *see* "Subjects and Methods" section) or for the logrank test with events in the first *N* years after randomization discarded (truncated analysis).
†95% confidence interval for the estimated risk of active to placebo.
‡Two-sided.

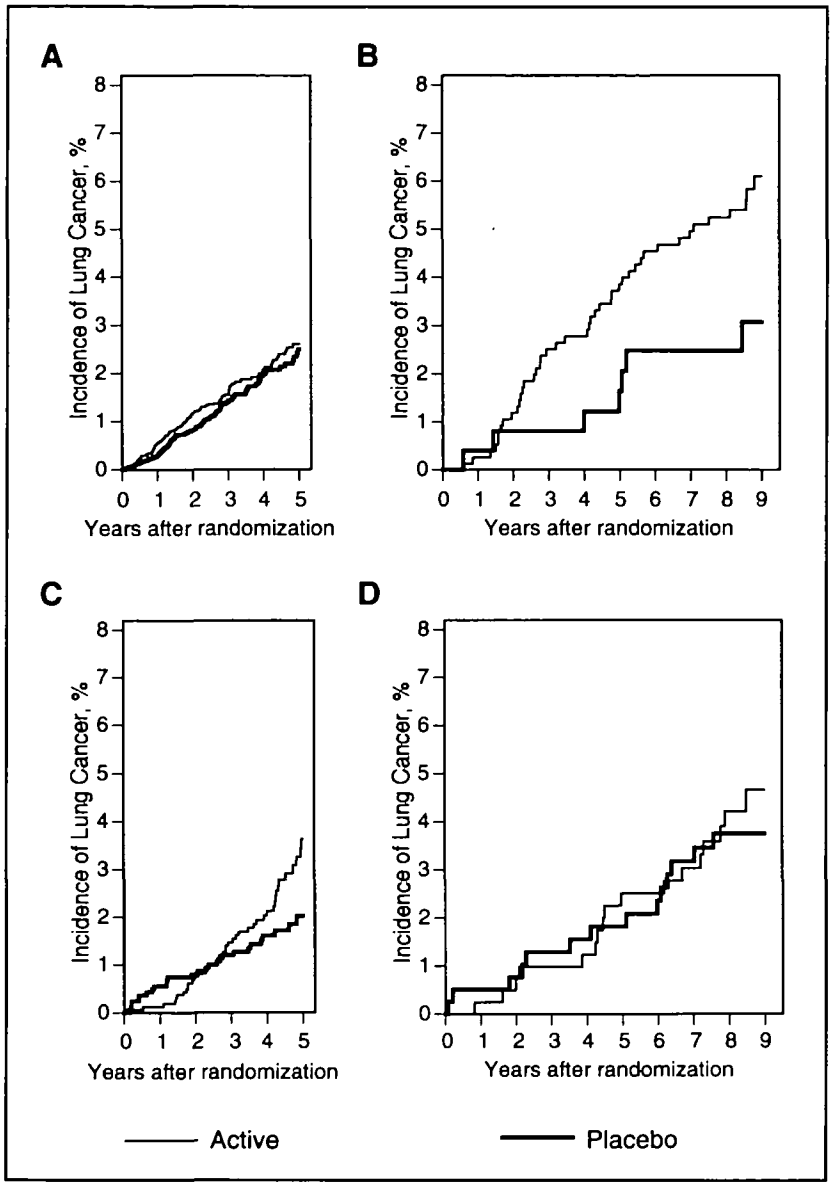

Fig. 1. Cumulative incidence of lung cancer. Active = the daily combination of 30 mg β-carotene and 25 000 IU retinyl palmitate. A) Efficacy cohort: heavy smokers. B) Pilot cohort: heavy smokers. C) Efficacy cohort: asbestos-exposed participants. D) Pilot cohort: asbestos-exposed participants. Data are shown only through 5 years of follow-up for efficacy participants and 10 years of follow-up for pilot participants because of the small number of participants beyond those times. Compare with similar plots for total CARET population [Fig. 1 in (*8*)].

Endpoints Monitoring Committee, beginning with the first interim analysis, coincident with publication of ATBC results. The truncation analyses showed high point estimates for the RRs after the first 3 or 4 years; the weighted analyses showed steadily increasing RRs with longer periods of weighting to full effect. These analyses suggest that the effect of the active vitamins in the total CARET population was greatest several years after we began their administration. Moreover, they suggest that the differences between the placebo and active treatment groups were not due to unrecognized differences between the groups in lung cancer risk at randomization.

Cigarette Smoking Status and Alcohol Consumption

Both the heavy smokers and asbestos-exposed populations included current and former smokers at base line, recruited to seek evidence of possible differences in response. Among the 132 never smokers recruited in the asbestos pilot study, there were no lung cancers. Table 2 displays unweighted and weighted lung cancer RRs by various measures of smoking status. Subgroups of particular interest were current and former smokers in the heavy smoker population, which did not have the possibly confounding effect of asbestos exposure. Within this group, the simplest comparison was of those who were current smokers at randomization (unweighted RR = 1.42, 95% CI = 1.07-1.87, and $P = .01$; weighted RR = 1.37, 95% CI = 0.98-1.91, and $P = .06$) and those who were former smokers at randomization (unweighted RR = 0.80, 95% CI = 0.48-1.31, and $P = .37$; weighted RR = 0.80, 95% CI = 0.44-1.45, and $P = .46$). With no adjustment for multiple tests, the test for a quantitative difference in intervention effect between current and former smokers in the heavy smoker population was statistically significant ($P = .03$), but the test for a qualitative interaction of intervention and smoking status (*see* "Subjects and Methods" section) was not ($P = .19$), reflecting the fact that the CI about the 0.80 RR in former smokers included RRs greater than 1. Because of the multiple tests performed, this result can be considered only to raise the hypothesis that the response to the study vitamins in former smokers with no asbestos exposure may not be adverse and might even be favorable.

The level of self-reported base-line alcohol intake, from the food-frequency questionnaires, was analyzed as an independent variable and in combination with smoking and with base-line β-carotene/retinol levels; 876 participants, including 45 with lung cancer, did not complete a CARET food-frequency questionnaire from which alcohol intake could be assessed, generally because they were members of the pilot studies who did not continue active involvement in CARET. Overall, 35% of CARET participants reported no alcohol intake (33% among males and 39% among females). Table 4 presents lung cancer incidence rates using sex-specific levels of alcohol intake. The test for heterogeneity of risk from the intervention among the first four levels in Table 4 was statistically significant ($\chi_3^2 = 10.6$; $P = .01$). The difference in the intervention RR between the highest quartile of alcohol intake (RR = 1.99; 95% CI = 1.28-3.09) and nondrinkers (RR = 1.07; 95% CI = 0.76-1.51) was statistically significant ($P = .02$). Because of the lack of a consistent dose–response effect and the multiple tests performed, we considered this result to be only suggestive. There was no evidence that, within the highest quartile of alcohol intake, those with alcohol intake above the 85th or 95th percentile were at still higher risk (Table 4). There was a statistically highly significant association of alcohol intake with smoking status; current smokers reported 20%-25% higher alcohol intake than former smokers among both males and females and four times higher intake than the small number of never smokers in the asbestos-exposed population (data not shown). This association, however, does not explain the effects seen in Table 4; with Cox regression, the most parsimonious model included an intervention group by alcohol quartile interaction ($P = .015$) and a main effect for smoking status ($P = .0001$) but no evidence of smoking by alcohol interaction effect on incidence of lung cancer ($P = .88$). The distribution of reported alcohol use by smoking status in males was similar between our smoker and asbestos-exposed populations.

Base-line Serum β-Carotene Concentrations

Table 5 shows the inverse association of base-line serum β-carotene concentrations with lung cancer incidence during CARET. In all participants (RR = 0.69; 95% CI = 0.54-0.88; $P = .003$) and in smokers (RR = 0.62; 95% CI = 0.46-0.82; $P = .0008$), there was a statistically significant inverse association. There was a slight trend in the same direction in the asbestos-exposed population. The point estimate of the RR of those above versus those below the median of base-line serum β-carotene concentrations was the same for those randomly assigned to placebo (0.69) or active vitamins (0.69) in the total CARET population, within the asbestos-exposed and smoker study populations, and, within smokers, between current and former smokers. Similar effects were seen in the analysis of the dietary intake of β-carotene, based on the CARET food-frequency questionnaires at base line (data not shown). Thus, base-line β-carotene status did not modify the elevated RRs associated with active vitamins in any of the analyses presented in this article.

Histologic Classification

Table 6 summarizes the RRs of active to placebo groups by histologic type (*see* "Subjects and Methods" section). The data are suggestive that the adverse effect associated with the active vitamins is greatest for large-cell lung cancer, although the test for heterogeneity in the RR was not statistically significant ($\chi_4 2 = 4.41$; $P = .35$). There were no statistically significant differences in the distributions of histologic types between males and females (data not shown), all of whom were current or former smokers. By comparison, the lung cancer diagnoses in the ATBC study were 17% adenocarcinoma, 45% squamous cell carcinoma, 25% small-cell carcinoma, and 13% other, including large-cell carcinoma (*10*).

Lung Cancer Mortality

Analyses of lung cancer mortality for CARET participants showed an RR associated with the active study vitamins of 1.59 (95% CI = 1.13-2.23; $P = .01$) with 2-year linear weighting and an RR of 1.46 (95% CI = 1.07-2.00; $P = .02$) unweighted. Survival time after diagnosis was nearly identical between the ac-

Table 4. Number of lung cancers by base-line alcohol intake, lung cancer incidence rates, and relative risks and 95% confidence intervals

	Events*/No. randomly assigned		Incidence rate, ×1000		Unweighted analysis		Weighted analysis	
Subgroup	Active†	Placebo	Active†	Placebo	Relative risk‡	95% confidence interval§	Relative risk‡	95% confidence interval§
Nondrinkers‖	68/3054	63/3067	5.5	5.3	1.07	0.76-1.51	1.21	0.80-1.83
Drinkers								
Below median of alcohol intake¶	29/1301	16/1296	5.4	3.1	1.71	0.92-3.17	1.97	0.95-4.07
Third quartile of alcohol intake¶	35/2284	39/2073	3.8	4.9	0.79	0.50-1.26	0.75	0.44-1.30
Fourth quartile of alcohol intake¶	64/2267	29/2096	7.1	3.7	1.99	1.28-3.09	1.98	1.19-3.31
>30 g/day alcohol, about 85th percentile	43/1400	20/1300	7.7	4.1	1.90	1.11-3.24	2.02	1.07-3.80
>50 g/day alcohol, about 95th percentile	21/666	9/575	7.9	4.3	1.57	0.70-3.51	1.65	0.64-4.23

*Participants diagnosed with lung cancer who completed a valid food-frequency questionnaire.

†Active = the daily combination of 30 mg β-carotene and 25 000 IU retinyl palmitate.

‡Estimated relative risk of active to placebo stratified on high-risk population, cohort, and study center, for the logrank test (unweighted analysis) and for the Cox regression model with time-dependent covariate (weighted analysis; *see* "Subjects and Methods" section).

§95% confidence interval for the estimated relative risk of active to placebo.

‖33% of males and 39% of females reported no alcohol intake.

¶Percentiles of alcohol intake for males are median 3.0 g/day and 75th percentile 18.7 g/day; for females, they are median 1.2 g/day and 75th percentile 11.1 g/day. An alcoholic drink contains approximately 15 g alcohol.

Table 5. Numbers of lung cancers by base-line serum β-carotene concentrations above versus below the median*

CARET† population group	No. of lung cancers‡		Unweighted analysis		
	Serum β-carotene above median	Serum β-carotene below median	Relative risk above/below median§	95% confidence interval‖	P¶
All participants	113	162	0.69	0.54-0.88	.003
Randomly assigned to placebo	45	64	0.69	0.47-1.02	.06
Randomly assigned to active#	68	98	0.69	0.50-0.94	.02
Asbestos-exposed participants	32	46	0.95	0.60-1.49	.81
Randomly assigned to placebo	13	20	0.88	0.43-1.77	.71
Randomly assigned to active#	19	26	0.96	0.52-1.76	.90
Heavy smokers	81	116	0.62	0.46-0.82	.0008
Randomly assigned to placebo	32	44	0.63	0.40-0.99	.04
Randomly assigned to active#	49	72	0.62	0.43-0.89	.01
Current smoker at base line	59	92	0.62	0.45-0.86	.004
Randomly assigned to placebo	21	31	0.63	0.36-1.09	.10
Randomly assigned to active#	38	61	0.63	0.42-0.95	.03
Former smoker at base line	22	24	0.69	0.39-1.24	.21
Randomly assigned to placebo	11	13	0.63	0.28-1.40	.25
Randomly assigned to active#	11	11	0.72	0.31-1.69	.45

*Median β-carotene concentration = 152 ng/mL.
†Beta-Carotene and Retinol Efficacy Trial.
‡Participants diagnosed with lung cancer who had a base-line serum β-carotene concentration.
§Estimated relative risk above the median serum β-carotene concentration to below the median serum β-carotene concentration for the logrank test stratified on risk population, cohort, and study center.
‖95% confidence interval for the estimated relative risk above to below the median serum β-carotene concentration.
¶Two-sided.
#Active = the daily combination of 30 mg β-carotene and 25 000 IU retinyl palmitate.

tive and placebo arms, with the unweighted RR of active to placebo of 1.05 (95% CI = 0.80-1.37; $P = .71$).

Other Cancers

Finally, we examined the incidence of other cancers in the two intervention groups. There were no statistically significant differences (Table 7) for any of eight common cancer types, including smoking-related sites (urinary bladder and head and neck), or for the aggregate. The 23 cases of mesothelioma were distributed 14 versus nine (active versus placebo), with 21 of the cases among the asbestos-exposed and two among the smoker population (one of whom would have met the eligibility criteria for the asbestos-exposed cohort). The large RR for leukemia was based on only 26 cases.

Discussion

The CARET findings of excess lung cancers and excess deaths in the intervention group receiving β-carotene and vitamin A, including the 23% excess in lung cancers in male smokers, confirm results reported in 1994: The ATBC trial in 29 133 male smokers in Finland found an 18% excess of lung

Table 6. Numbers of lung cancers by histologic type, logrank P values, estimated relative risks, and 95% confidence intervals, with and without downweighting*

Histologic type	No. of lung cancers†			Unweighted analysis			Weighted analysis		
	% of total cases	Active	Placebo	Relative risk‡	95% confidence interval§	P‖	Relative risk‡	95% confidence interval§	P‖
Adenocarcinoma	30	52	43	1.01	0.67-1.53	.96	1.25	0.76-2.06	.37
Squamous cell carcinoma	23	42	31	1.27	0.80-2.03	.31	1.37	0.78-2.39	.27
Small-cell carcinoma	19	33	27	1.07	0.64-1.80	.79	0.88	0.48-1.63	.69
Large-cell carcinoma	20	44	19	1.89	1.09-3.26	.02	2.20	1.13-4.27	.02
Other	8	14	11	1.19	0.54-2.63	.67	1.03	0.40-2.62	.95

*Number randomly assigned: 9420 active (i.e., the daily combination of 30 mg β-carotene and 25 000 IU retinyl palmitate); 8894 placebo.
†316 lung cancer cases with Beta-Carotene and Retinol Efficacy Trial pathologist review; other includes 11 adenosquamous, six non-small cell, three unable to classify, and one each for basaloid, carcinoid, carcinosarcoma, combined small-cell and squamous cell, and mixed small-cell/large-cell (*see* "Subjects and Methods" section).
‡Estimated relative risk of active to placebo stratified on high-risk population, cohort, and study center, for the logrank test (unweighted analysis) and for the Cox regression model with time-dependent covariate (weighted analysis; *see* "Subjects and Methods" section).
§95% confidence interval for the estimated relative risk of active to placebo.
‖Two-sided.

Table 7. Numbers of cancers other than lung cancer by treatment arm, *P* values, estimated relative risks, and 95% confidence intervals

Cancer type*	Events/No. randomly assigned		Unweighted analysis		
	Active†	Placebo	Relative risk‡	95% confidence interval§	*P*‖
Urinary bladder (ICD-O 188)	42/9420	36/8894	1.08	0.69-1.70	.73
Breast (ICD-O 174)	59/3208	65/3081	0.78	0.55-1.12	.18
Colorectal (ICD-O 153, 154)	56/9420	50/8894	1.02	0.70-1.50	.91
Head and neck (ICD-O 141, 143-149, 161)	32/9420	22/8894	1.26	0.73-2.19	.41
Leukemia (histology¶ 9800-9940)	18/9420	8/8894	2.18	0.95-5.03	.06
Lymphoma (histology¶ 9590-9699, 9750)	13/9420	13/8894	0.91	0.42-1.98	.81
Mesothelioma (histology¶ 9050-9053)	14/9420	9/8894	1.52	0.66-3.52	.32
Prostate (ICD-O 185)	161/6212	139/5813	1.01	0.80-1.27	.95

*ICD-O = International Classification of Diseases for Oncology (*11*).
†Active = the daily combination of 30 mg β-carotene and 25 000 IU retinyl palmitate.
‡Estimated relative risk of active to placebo for the logrank test stratified on high-risk population, cohort, and study center.
§95% confidence interval for the estimated relative risk of active to placebo.
‖Two-sided.
¶Provided primary site classification is not one of the ICD-O categories listed in this table.

cancer in participants receiving β-carotene (*19*), now updated to a 16% excess (*10*). Vitamin E had no effect and showed no interaction with β-carotene in the ATBC study. The ATBC finding was largely dismissed by those confident that the β-carotene was responsible for the inverse association of fruit and vegetable intake with lung cancer risk (and heart disease risk, as well) in the epidemiologic literature. With these detailed results from CARET, the combined weight of the evidence is highly consistent and troubling.

Both asbestos-exposed and smoker populations in the pilot and efficacy cohorts of CARET had RRs for lung cancer incidence of 1.10 or higher. At this time of follow-up, there was considerable heterogeneity across these four subgroups (Table 2; Fig. 1). The nonstatistically significant finding that the RR of lung cancer was about 0.8 in former smoker subgroups given the active study vitamins is encouraging with regard to a possible benefit for those who quit smoking, but it must be considered in light of the large number of subanalyses performed. We are conducting a further follow-up.

The point estimates of the excesses of lung cancers and of deaths in CARET were larger than in ATBC (although the CIs have wide overlap), primarily reflecting the more extreme results in the asbestos-exposed subpopulation. Given CARET's design, it was not possible to determine if the coadministration of retinyl palmitate affected the RR. The unweighted RR in the subpopulation of male CARET current smokers, excluding those exposed to asbestos, was 1.39. The fact that each of the four major subgroups had an RR of 1.10 or greater, the striking excess mortality from all causes and from cardiovascular causes (*8*), and the previously reported ATBC results were taken into consideration when the CARET Safety and Endpoints Monitoring Committee recommended and the Steering Committee decided on January 11, 1996, to stop the intervention.

The Physicians' Health Study concluded its scheduled intervention with 50 mg β-carotene on alternate days after a mean follow-up of 12 years in December 1995; the RR was 1.0 for total epithelial cancers and for all-cause and cardiovascular mortality (*20*), consistent with no benefit and no harm. It should be emphasized that the Physicians' Health Study had limited power to detect an adverse effect on lung cancer incidence in its population at very low risk with only 11% current smokers. When the Physicians' Health Study and CARET results became known, β-carotene was withdrawn from the ongoing Women's Health Study of 40 000 female health professionals (*21*), who are now receiving just vitamin E and/or vitamin C. The Women's Antioxidant Cardiovascular Study (*22*) in 8000 women with cardiac risk factors that made them ineligible for the preceding study (*21*) is still administering β-carotene with or without vitamin E with or without vitamin C.

We considered the feasibility of continuing the active intervention in former heavy smokers only (plus current smokers who quit and stay quit for 12 months). However, the all-cause mortality picture for the former smokers was not encouraging (RR of 1.06 for all-cause mortality, compared with RR of 1.15 for current smokers), the RR was high among asbestos-exposed former smokers (Table 2), the message of termination for current smokers and continuation for former smokers would be complicated, and the statistical power would be quite limited. Thus, this plan had to be abandoned.

As in numerous observational epidemiologic studies and in ATBC, we observed an inverse association between base-line β-carotene dietary intake estimates and serum levels and later lung cancer incidence. β-Carotene (and vitamin A) administration in CARET raised the serum β-carotene levels 12-fold from the base line. It is conceivable that such levels are toxic or at least cause serious dysequilibrium with other compounds important to redox relationships or other cellular mechanisms. We measured the serum levels of vitamin E in CARET participants and found no difference by treatment arm (*23*). Despite a report that β-carotene drastically lowered vitamin E serum levels (*24*), we and three other groups (*19,25,26*) now have found no such effect. We are investigating possible effects on other carotenoids and on folic acid; other investigators (*27*) have reported that intake of β-carotene supplements lowers serum lycopene concentrations but not the concentrations of other carotenoids. There is no basis to believe that synthetic β-carotene in supplements is chemically or biologically different from β-carotene in fruits and vegetables; in both, the β-carotene is greater than 90%

all-*trans* with traces of 9-*cis* and 13-*cis* isomers (*27,28*). Algal sources of β-carotene have about equal proportions of all-*trans* and 9-*cis* β-carotene; however, after absorption and bioisomerization, isomers in the human circulation are very similar to those from synthetic β-carotene (*27*).

What might be a biologic basis for an adverse effect of β-carotene and/or retinyl palmitate? The interaction of the chemicals in cigarette smoke, antioxidants in the respiratory tract fluids, and epithelial lung cells is complex and poorly understood (*29*). The antioxidant effects of β-carotene are actually quite dependent on assay method and generally not too potent (*30*); lycopene and α-carotene are now thought to have a greater antioxidant effect (*31*). β-Carotene can function as a pro-oxidant under certain conditions of oxygen tension and high solute concentration (*28,30,32-34*). Since β-carotene is very poorly soluble in water, its concentration in physiologic media and in cell compartments is quite uncertain; inside lipoprotein particles or cellular membranes, the microenvironmental conditions may give β-carotene unpredictable properties. The free-radical-rich atmosphere produced by the chemicals in cigarette smoke and the resultant inflammatory response in the lung with generation of complex secondary reactive oxygen and nitrogen species enhance the prospect for the formation of unusual β-carotene oxidant and other reactive species (*30,34*). These compounds may serve as powerful chemical messengers with resultant cell proliferation, in addition to oxidizing proteins, lipids, and nucleic acids (*35*). Retinyl palmitate itself, although generally demonstrated to be an enhancer of differentiation at physiologic concentrations, could have adverse genomic effects in carcinogen-altered epithelial cells; congenital abnormalities have been associated with modest doses of vitamin A in a recent epidemiology study (*36*). Studies of the pathophysiology and biochemistry of β-carotene and retinyl palmitate in carcinogen-altered epithelial cells in vitro and in vivo (*37*) may prove informative.

A pooled analysis of the very similar ATBC and CARET populations and interventions shows an RR for lung cancer of 1.20 (95% CI = 1.07-1.33), based on RRs of 1.16 with 894 participants developing lung cancer among the 29 133 male smokers in ATBC (*10*) and 1.28 with 388 participants developing lung cancer among the 18 314 smokers and asbestos-exposed smokers in CARET, by use of unweighted analyses. If the Physicians' Health Study result (*20*) of a lung cancer RR of 0.93 (based on 170 total participants with lung cancer) is added, the pooled RR becomes 1.16 (95% CI = 1.05-1.29). For all-cause mortality, with 3570 ATBC deaths and 974 CARET deaths, the pooled RR is 1.10 (95% CI = 1.04-1.17); with the 1947 deaths in the Physicians' Health Study added, the pooled RR is 1.07 (95% CI = 1.02-1.12).

The present findings provide ample grounds to discourage use of supplemental β-carotene and the combination of β-carotene and vitamin A and to require proof of safety and efficacy before advocating use of vitamin supplements, consistent with recent recommendations of the Presidential Commission on Risk Assessment and Risk Management (*38*). The search for effective chemopreventive agents will go on, with a better appreciation that large-scale, randomized trials are essential to determine not only efficacy but also safety. In the meantime, we must rely on smoking cessation, prevention of smoking, and reduction of exposures to known occupational and environmental carcinogens (*39*) to prevent lung cancer. Nevertheless, we continue to recommend consumption of fruits and vegetables, at least for their high fiber and low fat contents.

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Notes

Supported by Public Health Service grants U01CA63673, U01CA63674, U01CA47989, U01CA48200, U01CA48203, U01CA48196, and U01CA52596 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

B. Valanis holds stock in Hoffmann-La Roche, Inc., which manufactures the dietary supplement β-carotene used in this CARET study.

We thank our partners—the CARET participants, staff, and investigators; the members of the CARET Safety and Endpoints Monitoring Committee (Anthony Miller, Robert Bruce, Julie Buring, Frank Iber, and O. Dale Williams); and our National Cancer Institute program officers (Carlos Caban and Marjorie Perloff).

Manuscript received May 17, 1996; revised July 29, 1996; accepted August 19, 1996.