A Study of the Effects of Beta-Carotene Supplementation on Serum Levels of Beta-Carotene and Vitamin E.

Summary

This double-blinded study included forty-six volunteers, who were randomized into one of 5 dose groups of beta-carotene (0, 15, 30, 45, or 60 mg/day), and received beta-carotene supplementation over a 9-month period. The primary goal was to determine the dose response relationship of beta-carotene supplementation by comparing dose groups with respect to plasma beta-carotene levels at 3 and 9 months after randomization. Secondarily, there was an interest in comparing dose groups with respect to plasma vitamin E levels.

We used two sample t-tests for unequal variances to compare dose groups with respect to 3-month and 9-month changes in serum beta-carotene and vitamin E levels from baseline. The results of the study indicate that subjects in dose groups 15, 30, 45, and 60 mg/day had statistically significant higher 3-month and 9-month increases in beta-carotene levels, when compared to the placebo group. Participants given 15 mg/day of beta-carotene had a 923.0 (95% CI: 468.1-1378.0, P < .0001) higher 3-month mean change in serum beta-carotene levels from baseline, and an 1149.7 (95% CI: 132.9-2166.6, P = .0006) higher 9-month mean change in serum beta-carotene levels from baseline. Point estimates suggest a potential general trend for increasing dose beyond 15 mg/day resulting in higher 3-month and 9-month increases in beta-carotene levels, but none of these differences were statistically significant. Future studies may want to further address this potential trend, if the estimated increases in beta-carotene levels in the blood with increased dose are clinically important.

There were no statistically significant differences between dose groups with respect to either 3-month or 9-month change in vitamin E serum levels from baseline. We do note that point estimates suggest a potential general trend for beta-carotene dose levels 15, 30, 45, and 60 mg/day to be associated with greater decreases in vitamin E levels at 9 months from baseline, as compared to the placebo group. We believe this potential trend could be related to both beta-carotene and vitamin E being lipid soluble compounds, and is of scientific interest due to the value of vitamin E as an important nutrient for the body. This potential effect of beta-carotene supplementation may warrant further exploration in future studies, where an increased sample size and a more focused study aim could add precision to the analysis.

Comment [A1]: Overall goal?

Comment [A2]: Lack of statistical significance does not imply lack of interest in estimates, CI, and p values! If it is worth commenting on such a trend, it is worthwhile providing the estimates.

Comment [A3]: And again! Review the lectures on the role of CI vs p values in scientific investigations. Statistical significance is something to consider, but it is not the only issue by a long shot.

Background

Beta-carotene is a common nutrient found in many foods, including green and yellow fruits and vegetables. It is the most nutritionally active carotenoid, comprising 15-30% of total serum carotenoids [1]. Among the various roles that this nutrient plays in the body, the possible beneficial effect of beta-carotene supplementation as a means of protection against cancer has recently been revealed [2]. This association between beta-carotene supplementation and cancer reduction has been found to be particularly strong among lung cancer patients. Several studies have shown that, in patients suffering from lung cancer, vitamin E and beta-carotene levels are lower than their age- and sex-matched healthy controls.[3,4,1] Beta-carotene supplementation also has an effect on serum levels of vitamin E, due to the fact that both nutrients are lipid-soluble, and thereby may fight for the same biological space [5]. It is well known that vitamin E is also an essential nutrient, one of its primary roles being the enhancement of cell-mediated and humoral immunity [5], in addition to its role in promoting neural and dermal health. Although patients with early, slight deficiency of vitamin E are generally asymptomatic, severe vitamin E deficiency can cause neurological symptoms. Specifically, a long term, severe vitamin E deficiency may cause a spinocerebellar syndrome, with neuropathy, in adults as well as in children [19]. Therefore, the effect of beta-carotene supplementation on vitamin E is also a relevant topic when investigating beta-carotene supplementation and its effects. Since both beta-carotene and vitamin E are lipid soluble vitamins, serum levels of these nutrients are affected by dietary fat intake and response to serum lipid levels. [6,7]

Comment [A4]: Has this really been established? Did they study supplementation or dietary sources of beta carotene. And how do you study cancer reduction in lung cancer patients? Did they look at tumor regression, or were they really looking at cancer incidence in a general population containing both cancer patients and patients without cancer?
I have only looked at the abstract of your second reference, but it seems to talk about dietary beta carotene, not supplementation. And it (in a summary statement that was as vague as the ones I complained about above) did not find any statistically significant association between dietary beta carotene and breast cancer risk.

The standard dosage given in beta-carotene supplementation studies has been found to vary from 12 to 180 mg/day. One study showed that 15 mg/day resulted in substantial serum response with no skin discoloration or toxicity [9]. After supplementation, beta-carotene concentrations in serum usually reach a plateau after 1.5 to 4 weeks, although there is much individual variation [10]. It is important to note that one study documented substantial interindividual heterogeneity in beta-carotene serum concentrations after beta-carotene supplementation, perhaps due to the dietary factors or efficiency of carotenoid absorption [11]. High levels of beta-carotene have not been shown to have toxic effects on the body, with the only outward symptom being occasional yellowing of the skin (xanthosis) [16,17,18].

The data for this study was analyzed with the main goals of a Phase II prevention trial in mind, with the primary goal being an evaluation of the dose-response relationship of the drug. Therefore, we were interested in comparing the different doses of beta-carotene supplementation with respect to their effect on levels of serum beta-carotene in the blood at specific time points. In addition, as a Phase II trial, there was also a concern for potential toxicity risks associated with the drug. Thus, there was an interest in comparing dose groups to assess whether increased dose level of beta-carotene supplementation influenced levels of vitamin E, an important nutrient, in the blood. The information obtained from this trial would then help the beta-carotene supplement to be moved forward to Phase III testing, where the efficacy of the drug as a cancer preventive agent could be explored rigorously.

Question of Interest

The specific aim of the client was to determine how different dose levels affected serum beta-carotene levels in the blood after three and nine months of beta-carotene supplementation. In particular, we were interested in the dose response relationship of serum beta-carotene following beta-carotene supplementation, with different dose levels of beta-carotene being compared against the placebo dose and against each other as well. In addition, we were interested in comparing vitamin E serum levels across dose groups, at both 3 months and 9 months after randomization. However, due to data collection constraints, we are unable to analyze the effect of beta-carotene supplementation on any other blood chemistries as the client had stated in their study documentation. There was also a general interest to explore the affect of dose level on the buildup of beta-carotene over time, but we decided to focus on the specific aim of the study to compare dose levels with respect to three and nine month levels of serum beta-carotene.

Source of the Data

This data has been obtained from the results of a Phase II prevention trial where 46 volunteers of unspecified health status were assigned to dose groups in a double-blind fashion. Beta-carotene supplementation was given over a 9-month time period, and serum beta-carotene and vitamin E levels were assessed at randomization as well as three and nine months after the trial had begun. No units for serum beta-carotene or vitamin E levels were provided in the study documentation. Six patients had missing data for vitamin E and beta-carotene at 9 months, and one patient had missing data for vitamin E and beta-carotene at 3 months. Of the six who had missing data for 9 months one was in each of the dose groups 0, 15, 45, 60 and 2 were in the dose group 30 mg/day. Thus there was no apparent pattern of missing values across dose groups. Additional measurements taken on participants include: weight at randomization in pounds, body mass index, serum cholesterol at randomization, and percent body fat at randomization. Previous studies have adjusted for measured variables percent body fat, cholesterol, BMI, sex and age [20, 21, 22]. No stratified analyses were performed because of the small sample sizes in each dose group (all groups had less than or equal to 10 patients). Other variables that were not measured in this trial but have been shown to be confounders in other similar trials include: cigarettes smoked per day and alcohol usage [12,4,13,14,15]. Also not present are dietary information and serum triglycerides levels for patients in the trial, which have been found to affect serum beta-carotene.

Comment [A5]: Good to note. However, these really are results, so you should address this in the Results section (could it be that toxicity led to the missing data?).

Comment [A6]: And the relevance of this is….? (This is an RCT. In one sense I can say there can be no confounding. Of course with small sample sizes this could be of more concern. So this requires a bit more discussion, if you are going to go there. In any case, this is probably better for the discussion, rather than the methods for an RCT.

Statistical Methods

The primary outcomes of interest were serum beta-carotene and vitamin E levels at 3 and 9 months after randomization, with comparison across dose groups. Because there was only 1 missing value at 3 months and 6 missing values at 9 months, with the number of missing values similar across dose groups, we assumed missing values were non-informative and excluded them from the analysis. No transformations or interactions were motivated by any literature on serum beta-carotene or vitamin E. Descriptive statistics (Table 1) were calculated on the patient baseline characteristics sex, age, weight, percent body fat, cholesterol, and BMI. There were no striking differences in these characteristics across dose groups (no evidence of imbalances in randomization). Stratification by variables that have been adjusted for in previous analyses on serum beta-carotene was not employed here due to the small sample sizes in each dose group (all had 10 patients or less). Descriptive statistics (Table 2) were calculated on the outcomes of interest; 3-month, 9-month, and time-average patient levels of serum beta-carotene and serum vitamin E. There was no evidence of any noticeable outliers or skewness that would have potentially motivated transforming the outcome measures. In order to add precision, statistical inference was based on the change in serum level from baseline, as there was a pre-study assumption of high correlation between baseline and both 3 and 9 months levels of serum beta-carotene and vitamin E. Two sample t-tests (for unequal variances) for a difference between dose groups in mean changes from baseline (both at 3 months and at 9 months) in serum beta-carotene and in serum vitamin E were performed. Estimates of the true differences in mean change from baseline were provided, along with 95% adjusted confidence intervals indicating a range of possible values for each true difference for which the observed data would not be unusual. Two-sided P values were reported, with statistical significance determined at the 0.00125 level. The critical significance level of 0.00125, along with corresponding 95% adjusted confidence intervals, was used to account for the issue of multiple comparisons, as explained in greater detail below. Analyses were performed using Stata 10.0 software (STATA Corp., College Station, TX, 2007).

It is important to note that conducting multiple comparisons presented an important statistical issue in the analyses. The study was intended to compare the beta-carotene dose response in patients across the 5 different dose groups at 3 months and 9 months after randomization. Secondarily, it sought to compare dose groups with respect to vitamin E levels at 3 months and 9 months. In order to address these specific study aims, two- sample t tests were performed for all possible dose group comparisons, at each endpoint of interest. Because there were 40 two-sample t-tests assessed on this data set, a Bonferroni corrected critical P value of 1/40 * 0.05 = 0.00125 was used to determine statistical significance. Similarly, adjusted 95% confidence intervals were reported by calculating 99.875% intervals, corresponding to the 0.00125 critical P value. Performing so many comparisons was a limitation of the analysis. Generating a more focused specific study aim and thus limiting the comparisons in the statistical analysis may have allowed for more specific conclusions to be reached.

Other statistical methods could have been used to analyze the data from this study. For example, the primary inferential analysis could have been linear regression, which would have allowed for the inclusion of potential precision variables (sex, age, weight, percent body fat, cholesterol, BMI) in the model. A regression analysis would have added precision by allowing for an adjustment for baseline values rather than basing inferential tests on the change from baseline in the outcomes of interest, as was done here. However, the authors of the paper were not well versed in linear regression at the time of data analysis, and thus chose to perform two- sample comparisons.

Comment [A7]: These are results

Comment [A8]: This decision would have had to be made before looking at the data.

Comment [A9]: A valiant attempt, and something that is reasonable. You might imagine there is a huge loss of precicion with this approach, so we generally would not use this here. Next quarter we will talk about better approaches.

Results

Of 46 people randomized into the study who received at least one dose of beta-carotene, 8 were assigned to the dose 0 mg/day (placebo) group, 10 to the 15 mg/day group, 10 to the 30 mg/day group, 8 to the 45 mg/day group, and 10 to the 60 mg/day group. Of all participants, 52.17% (24/46) were female, and 47.83% (22/46) were male.

Baseline measurements of the study population can be seen in Table 1. Dose groups were similar in baseline characteristics age, weight, BMI, body mass index, cholesterol, percent body fat, and sex. The mean age of participants in the entire sample was 56.46, with a range of 50 to 65 years. Mean weight for participants was 165.46 pounds, with measurements ranging from 118 to 253 lbs, and mean BMI was 25.59 kg/m^2, with a range of 19.68 to 31.68kg/m^2. Mean percent body fat of participants was .30, with a range of .16 to .45. Mean cholesterol was 221.54 mg/dl, with cholesterol scores ranging from 159 mg/dl to 312.5 mg/dl.

The observed values in serum beta-carotene and vitamin E baseline levels were similar across dose groups, as seen in Table 2. An average baseline serum beta-carotene level of 222.35 was observed among all participants, with values ranging from 48.25 to 496, and an average baseline serum vitamin E level of 8.06 was found, with a range of 5.1 to 10.71.

The data indicate that subjects in dose groups 15, 30, 45, and 60 mg/day had statistically significant higher 3-month and 9-month increases in beta-carotene levels, when compared to the placebo group.

We estimate that participants given 15 mg/day of beta-carotene had a 923.0 (CI 468.1-1378.0) higher 3-month mean change in serum beta-carotene levels from baseline, and an 1149.7 (CI 132.9-2166.6) higher 9-month mean change in serum beta-carotene levels from baseline, when compared to subjects given placebo. Similarly, participants given 30 mg/day of beta-carotene had an 1109.7 (CI 792.0-1427.4) higher 3-month mean change in serum beta-carotene levels from baseline, and a 1382.2 (CI 689.8-2074.6) higher 9-month mean change in serum beta-carotene levels from baseline. Subjects given 45 mg/day had a 1035.8 (CI 729.8-1341.8) higher 3-month mean change in serum beta-carotene levels from baseline, and a 1623.8 mg/day (CI 578.1-2669.6) higher 9-month mean change in serum beta-carotene levels from baseline. Participants given 60 mg/day beta-carotene had a 1257.9 (CI 862.4-1653.4) higher 3-month mean serum beta-carotene levels from baseline and a 1743.7 (CI 1111.3-2376.1) higher 9-month mean serum beta-carotene levels from baseline, as compared to subjects in the placebo group.

Point estimates suggest a potential general trend for increasing dose beyond 15 mg/day resulting in higher 3-month and 9-month increases in beta-carotene levels, but none of these differences were statistically significant. When compared to subjects in the 15 mg/day dose group, participants given 30mg/day had a 186.7 (CI -287.1, 660.4) higher 3-month mean change and a 232.4 (CI -764.3, 1229.2) higher 9 month mean change in serum beta-carotene levels from baseline. Subjects given 45 mg/day had a 112.8 (CI -354.0, 579.5) higher 3 month mean change in serum beta-carotene levels from baseline and a 474.1 (CI -635.4, 1583.6) higher 9 month mean change in serum beta-carotene levels from baseline, as compared to the 15 mg/day dose group. Additionally, those given 60 mg/day had a 334.9 (CI -166.3, 836.1) higher 3 month mean change in serum beta-carotene levels from baseline and a 594.0 (CI -388.5, 1576.4) higher 9 month mean change in serum beta-carotene levels from baseline, as compared to the 15 mg/day dose group. Similar trends (not statistically significant) were observed when we compared the 30, 45 and 60 dose groups.

There were no statistically significant differences between dose groups with respect to either 3-month or 9-month change in vitamin E serum levels from baseline. (Figure 1, Table 3) However, point estimates show higher increases in vitamin E levels at 3 months and greater decreases in vitamin E levels at 9 months for dose groups 15, 30, 45 and 60 mg/day, as compared to the placebo group. There was no evidence of differences among dose groups 15, 30, 45, and 60 in 3-month or 9-month change in vitamin E levels.

Comment [A10]: A very minor comment: I would describe the sample, before I talked about how they were divided into dose groups

Comment [A11]: I would lead off with description, rather than inference.

First tell us about the range of measurements—we should be concerned about very low or very high values that might mean a few individuals were at risk for toxicity. You will not have statistical power to detect significant differences in the incidence of such high values, so description is all we have to go on.

And then focus on science first, statistics second. Provide estimates, then comment on statistical significance. It is possible to have large difference that we would be concerned about, yet not have stat significance. Or vice versa. The scientific measures are most important. Then comment on whether any such difference is merely compatible with random chance.

Comment [A12]: It is probably better to just list the most salient results, say for the 15 and 60 mg groups, and then let the able speak for itself.

Comment [A13]: You ought to be tired of me making this comment by now: Lack of statistical significance is not the final answer here. It was far more important to give the reader some clue about the size of difference for vit E for a couple groups (even though not stat signif) than it was to list all the comparisons for the beta carotene.

Discussion

The results of the study indicate that subjects in dose groups 15, 30, 45, and 60 mg/day had statistically significant higher 3-month and 9-month increases in serum beta-carotene levels, when compared to the placebo group. The lack of statistical significance among dose groups 15, 30 , 45 and 60 mg/day in changes in beta-carotene levels suggest that increasing does beyond 15 mg/day does not further

increase beta-carotene build up in the blood. However, point estimates suggest a potential general trend for increasing dose beyond 15 mg/day resulting in higher 3-month and 9-month increases in beta-carotene levels in the plasma. If deemed clinically important, future studies may want to further address this potential trend. Increased sample size and a more focused specific study aim (fewer comparisons) could add precision to the analysis and help detect these possible differences.

Although there were no statistically significant differences between dose groups with respect to either 3-month or 9-month change in vitamin E serum levels from baseline, the point estimates suggest a potential general trend for beta-carotene dose levels 15, 30, 45, and 60 to be associated with higher increases in vitamin E level at 3 months and greater decreases in vitamin E levels at 9 months from baseline, as compared to the placebo group. We believe this potential trend could be related to both beta-carotene and vitamin E being lipid soluble compounds, and should be considered for future studies, where an increased sample size could add precision to the analysis.

In addition, in future follow-up studies, it may be wise to examine how beta-carotene supplementation affects other blood chemistries such as electrolyte, serum triglyceride, and cholesterol levels, if at all. While cholesterol level was tested at baseline, it was not re-checked during the course of the study, which might have led to some of the observed, but statistically insignificant, measurements of beta-carotene and vitamin E. Serum triglycerides might have played a role in this too, but its effects were unknown as these two variables were untracked during the study period. As both vitamin E and beta-carotene are fat-soluble nutrients for which there is some relationship between fat intake (or serum lipids) and serum levels of the two vitamins, it would behoove studies to examine this potentially important effect modifier. It may also be worthwhile to track other fat soluble vitamin intake or serum levels, such as vitamin D, K and other sources of beta-carotene intake besides the beta-carotene intake, as dietary changes over the course of a year may affect the analysis because of the study length. Furthermore, rechecking serum lipid levels (via a full lipid panel) would also assist in the analysis.

There were significant limitations in the ability to stratify by subgroups in the study because of the small sample size. In future studies, it would be wise to have a larger sample size so that the effects of age, body mass index, sex, cholesterol level, and other variables (discussed later) can be examined for their effects on serum beta-carotene and vitamin E. Other variables which would be important to analyze based on the examination of other published journal articles to date include dietary fat intake and serum triglyceride levels. More important would be an analysis for potential confounding or effect modification around alcohol use and smoking status [16,19,20,23,32]. Many studies to date have shown sometimes dramatic effects on beta-carotene and vitamin E by smoking and alcohol use.

Although t-tests were performed in this analysis, the authors concede that other methods could have been used to test the scientific question of relevance. For example, regression could add precision to the testing model by adjusting for such variables in the data set as cholesterol, weight, age, BMI, percent fat, and sex.

Because of the length of the study and the dose levels involved (although beta-carotene overdose has not been shown to be toxic), adverse events should be tracked, especially since excess beta-carotene intake can cause yellowing of the skin, which could easily be confused for hepatitis or other medical conditions.

Since this was a phase II trial to determine the serum levels of beta-carotene following administration of fixed-dose levels, follow-up of participants was not continued after the end of the study. This was most likely a result of funding, but it would be scientifically interesting to follow patients past the end of the study and examine when the serum beta-carotene levels return to baseline. This would provide a better understanding of the dose-response relationship over time. In addition, it is not well known at what point in time the increased serum beta-carotene is achieved as patients were only tracked at three and nine months. During initial dosage, it would also be useful to measure serum vitamin A more frequently to determine the profile of beta-carotene loading.

Comment [A14]: WRONG. Lack of stat signif merely suggests that we were unable to prove a difference. You should make a distinction between "There is no difference" and "We were unable to prove there was a difference". I note that the sample size was too small to be able to show that the observed difference was definitive. If you were tryin to prove there was no difference, that would take an infinite sample size.

Comment [A15]: Well-stated.

You successfully avoided the trap of "with a larger sample size the results would have been statistically significant", which is a garbage statement.

Comment [A16]: I do, of course, have this data. You just did not have them.

Comment [A17]: I would agree with this statement, but you provided no data to suggest that this would be of interest or, indeed, that there was some mechanism whereby this might happen.

If you look at the SD of beta carotene at 9 mos versus 3 mos, you see that the highest dose groups had some individuals to go very high. Noting that tendency would have gone a long way toward making this suggestion more useful.

But I note that you did not even comment on the tendencies of the individual measurements, instead focusing only on the means.

Comment [A18]: Again: Is this just a general comment, or did you see anything that made you suspect that there were subpopulations with different results.

Comment [A19]: Justify your concern about confounding in an RCT. (you may have some legitimate concerns, but you did not give them).

Comment [A20]: And what is the scientific relevance of effect modification, should it exist?

Comment [A21]: And most especially baseline, since it is theoretically possible that your focus on the change in plasma levels actually led to decreased precision.

(In this data set, the correlation between carot0 and carot3 after adjusting for dose is estimated at r=0.46. With a true correlation below 0.5, you would have had marginally greater precision throwing the baseline variable away.)

Comment [A22]: Well, that is all that I gave you. I actually had monthly measurements. For what it is worth, the major change came before the 1 month measurement.

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Tables and Figures

Comment [A23]: It would have been far better to present separate tables for the pre- and post-randomization variables.

These tables do contain all the information, but it is way beyond what you would ever be able to print in a journal. Writing to a client, this might be useful, however.

Personally, I would have spend a bit more time making the presentation more concise. For the pre-randomization variables, the mean and SD are probably the only things that matter. For the post-randomization variables, we are in fact very interested in the min and max.

Treatment Group	N Miss	Mean	SD	Min	25th %ile	Median	75th %ile	Max
Age (yrs)								
Dose = 0 mg/day (N = 8)	0	56.25	4.30	52	52.5	55.5	59	64
Dose = 15 mg/day (N = 10)	0	56.3	4.64	50	52	56.5	60	62
Dose = 30 mg/day (N = 10)	0	57.2	4.08	50	55	57	60	64
Dose = 45 mg/day (N = 8)	0	55.88	3.14	51	54	55.5	58.5	60
Dose = 60 mg/day (N = 10)	0	56.5	5.21	52	52	54.5	61	65
Combined (N = 46)	0	56.46	4.20	50	53	56	60	65
Weight (lbs)								
Dose = 0 mg/day (N = 8)	0	180	32.83	118	164	179.5	207.5	220
Dose = 15 mg/day (N = 10)	0	167.8	36.84	118	126	174.5	204	213
Dose = 30 mg/day (N = 10)	0	151.8	30.21	123	129	140.5	175	204
Dose = 45 mg/day (N = 8)	0	172.63	40.85	126	146	163.5	191.5	253
Dose = 60 mg/day (N = 10)	0	159.4	19.10	126	153	160.5	172	190
Combined (N = 46)	0	165.46	32.43	118	138	164	190	253
BMI (kg/m^2)								
Dose = 0 mg/day (N = 8)	0	26.55	3.64	19.68	24.30	27.22	29.63	30.45
Dose = 15 mg/day (N = 10)	0	25.69	3.58	20.69	22.34	26.57	27.73	31.68
Dose = 30 mg/day (N = 10)	0	25.57	2.65	22.36	24.03	25.07	26.28	31.55
Dose = 45 mg/day (N = 8)	0	25.35	3.32	21.66	22.41	25.07	27.66	30.86
Dose = 60 mg/day (N = 10)	0	24.94	2.43	21.67	23.05	24.77	25.67	28.95
Combined (N = 46)	0	25.59	3.03	19.68	23.15	25.41	27.68	31.68
Cholesterol (mg/dl)								
Dose = 0 mg/day (N = 8)	0	217.75	28.50	190	202	211.5	221	283
Dose = 15 mg/day (N = 10)	0	223	29.72	171	201	223.5	254	265
Dose = 30 mg/day (N = 10)	0	213.2	33.49	159	183	214.5	239	268
Dose = 45 mg/day (N = 8)	0	213.31	33.54	169	185.5	212	239.75	263
Dose = 60 mg/day (N = 10)	0	238.05	38.88	209	210	219.5	243	312.5
Combined (N = 46)	0	221.54	33.10	159	202	216	239	312.5
Percent Body Fat								
Dose = 0 mg/day (N = 8)	0	0.28	0.08	0.17	0.23	0.26	0.34	0.42
Dose = 15 mg/day (N = 10)	1	0.28	0.09	0.16	0.22	0.27	0.32	0.45
Dose = 30 mg/day (N = 10)	0	0.30	0.06	0.22	0.25	0.31	0.36	0.37
Dose = 45 mg/day (N = 8)	0	0.32	0.06	0.27	0.28	0.30	0.37	0.43
Dose = 60 mg/day (N = 10)	0	0.30	0.09	0.18	0.20	0.33	0.37	0.43
Combined (N = 46)	1	0.30	0.08	0.16	0.25	0.31	0.36	0.45

Sex					
Treatment Group	N Miss	# Males	# Females	Percent Male	Percent Female
Dose = 0 mg/day (N = 8)	0	5	3	62.5	37.5
Dose = 15 mg/day (N = 10)	0	5	5	50	50
Dose = 30 mg/day (N = 10)	0	3	7	30	70
Dose = 45 mg/day (N = 8)	0	4	4	50	50
Dose = 60 mg/day (N = 10)	0	5	5	50	50
Combined (N = 46)	0	22	24	47.83	52.17

Table 1: Descriptive Statistics for Patient Characteristics by Treatment Group

Treatment Group	N Miss	Mean	SD	Min	25th %ile	Median	75th %ile	Max
Serum Beta-Carotene at Randomization								
Dose = 0 mg/day (N = 8)	0	270.24	136.29	136.25	148.08	227.75	398.88	476.25
Dose = 15 mg/day (N = 10)	0	220.06	127.94	64.75	136.00	185.63	237.75	496.00
Dose = 30 mg/day (N = 10)	0	219.35	83.85	125.50	140.00	205.00	282.25	348.50
Dose = 45 mg/day (N = 8)	0	226.98	105.54	93.25	147.92	216.38	299.13	395.75
Dose = 60 mg/day (N = 10)	0	217.81	122.34	48.25	98.25	224.29	310.75	407.50
Combined (N = 46)	0	229.35	112.54	48.25	140.00	212.00	310.75	496.00
Serum Beta-Carotene After 3 Months of Treatment								
Dose = 0 mg/day (N = 8)	0	243.52	94.34	109.33	179.67	220.50	327.25	384.00
Dose = 15 mg/day (N = 10)	0	1116.37	317.36	699.00	745.00	1203.00	1334.33	1602.67
Dose = 30 mg/day (N = 10)	0	1302.32	259.89	854.00	1172.00	1289.33	1540.50	1603.33
Dose = 45 mg/day (N = 8)	0	1236.04	239.34	860.50	1034.75	1343.25	1415.67	1440.50
Dose = 60 mg/day (N = 10)	1	1466.67	251.14	1098.00	1292.00	1410.33	1595.33	1959.67
Combined (N = 46)	1	1093.85	479.56	109.33	854.00	1255.33	1415.00	1959.67
Serum Beta-Carotene After 9 Months of Treatment								
Dose = 0 mg/day (N = 8)	1	186.32	87.80	84.50	126.00	149.00	286.00	323.00
Dose = 15 mg/day (N = 10)	2	1253.58	570.47	576.75	695.38	1250.00	1771.21	2018.75
Dose = 30 mg/day (N = 10)	1	1504.61	479.03	849.33	1157.33	1498.50	1840.00	2248.50
Dose = 45 mg/day (N = 8)	1	1749.08	579.05	950.25	993.00	1848.25	2247.67	2310.40
Dose = 60 mg/day (N = 10)	1	1877.63	429.88	1233.33	1724.67	1865.00	1917.67	2855.00
Combined (N = 46)	6	1350.42	734.48	84.50	799.67	1528.92	1914.67	2855.00
Time Average of Serum Beta-Carotene While on Treatment								
Dose = 0 mg/day (N = 8)	0	234.34	91.33	125.36	165.41	201.72	328.40	358.28
Dose = 15 mg/day (N = 10)	0	1131.81	319.87	712.91	827.36	1161.63	1430.35	1604.82
Dose = 30 mg/day (N = 10)	0	1336.67	271.89	937.72	1138.57	1246.40	1610.42	1702.72
Dose = 45 mg/day (N = 8)	0	1324.30	297.26	816.84	1144.18	1397.17	1529.65	1635.51
Dose = 60 mg/day (N = 10)	1	1522.56	249.53	1127.38	1443.22	1537.75	1582.95	2059.72
Combined (N = 46)	1	1130.15	506.66	125.36	827.36	1216.89	1537.75	2059.72
Serum Vitamin E at Randomization								
Dose = 0 mg/day (N = 8)	0	7.88	1.42	6.19	6.94	7.60	8.52	10.71
Dose = 15 mg/day (N = 10)	0	7.76	1.21	5.10	7.33	7.95	8.39	9.24
Dose = 30 mg/day (N = 10)	0	7.98	1.62	5.12	6.74	8.57	9.38	9.46
Dose = 45 mg/day (N = 8)	0	8.24	0.95	7.22	7.52	8.04	8.78	10.05
Dose = 60 mg/day (N = 10)	0	8.44	1.27	6.32	7.55	8.51	9.31	10.71
Combined (N = 46)	0	8.06	1.29	5.10	7.22	8.11	9.04	10.71
Serum Vitamin E After 3 Months of Treatment								
Dose = 0 mg/day (N = 8)	0	8.27	1.23	6.50	7.34	8.40	9.05	10.11
Dose = 15 mg/day (N = 10)	0	8.71	0.91	6.36	8.63	8.85	8.99	9.74
Dose = 30 mg/day (N = 10)	0	9.15	0.90	7.12	8.81	9.42	9.55	10.55
Dose = 45 mg/day (N = 8)	0	8.98	0.63	7.89	8.69	8.81	9.58	9.78
Dose = 60 mg/day (N = 10)	1	9.11	0.66	8.07	8.57	9.26	9.61	10.02
Combined (N = 46)	1	8.86	0.91	6.36	8.57	8.90	9.54	10.55
Serum Vitamin E After 9 Months of Treatment								
Dose = 0 mg/day (N = 8)	1	7.25	1.13	5.26	6.72	7.23	7.90	8.93
Dose = 15 mg/day (N = 10)	2	5.75	0.50	4.61	5.71	5.84	6.02	6.28
Dose = 30 mg/day (N = 10)	1	6.30	1.14	4.31	5.61	6.20	7.49	7.74
Dose = 45 mg/day (N = 8)	1	6.15	0.88	4.94	5.22	5.95	7.01	7.05

Dose = 60 mg/day (N = 10)	1	6.32	1.12	4.87	5.52	5.93	7.20	8.06
Combined (N = 46)	6	6.33	1.05	4.31	5.63	6.02	7.19	8.93
Time Average of Serum Vitamin E While on Treatment								
Dose = 0 mg/day (N = 8)	0	7.79	1.12	6.06	7.19	7.82	8.30	9.68
Dose = 15 mg/day (N = 10)	0	7.97	0.86	5.99	7.68	7.97	8.30	9.32
Dose = 30 mg/day (N = 10)	0	8.36	1.12	5.59	8.26	8.58	9.06	9.52
Dose = 45 mg/day (N = 8)	0	8.04	0.49	7.26	7.66	8.09	8.44	8.66
Dose = 60 mg/day (N = 10)	1	8.35	0.74	7.37	8.13	8.17	9.04	9.59
Combined (N = 46)	1	8.11	0.89	5.59	7.68	8.17	8.65	9.68

Table 2: Descriptive Statistics for Outcomes by Treatment Group

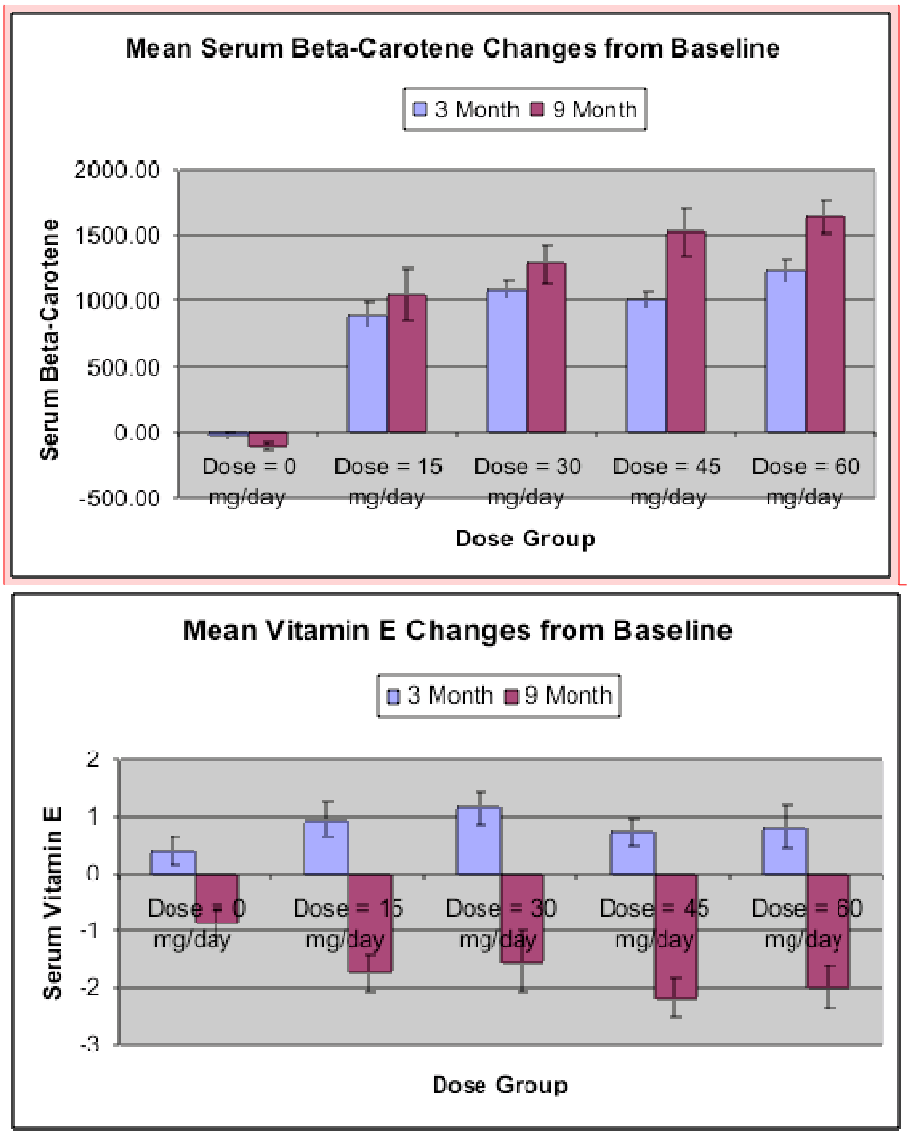
Comment [A24]: I like this table. I note that it is a little confusing to combine unadjusted P values with adjusted CI, though I actually prefer that approach, because multiplying p values by 40 leads to nonsensical results quite often.

Next quarter we will look at better approaches.

TABLE 3 T-tests[1,2] for change[3] from baseline by dose levels

T-test groups		β-carotene					
		Difference in three month change from baseline			Difference in nine month change from baseline		
Dose	Comparison dose	Point Estimate	95% CI	p-value	Point Estimate	95% CI	p-value
0	15	923.0	(468.1, 1378.0)	<0.0001	1149.7	(132.9, 2166.6)	0.0006
	30	1109.7	(792.0, 1427.4)	<0.0001	1382.2	(689.8, 2074.6)	<0.0001
	45	1035.8	(729.8, 1341.8)	<0.0001	1623.8	(578.1, 2669.6)	0.0001
	60	1257.9	(862.4, 1653.4)	<0.0001	1743.7	(1111.3, 2376.1)	<0.0001
15	30	186.7	(-287.1, 660.4)	0.1418	232.4	(-764.3, 1229.2)	0.3553
	45	112.8	(-354.0, 579.5)	0.3480	474.1	(-635.4, 1583.6)	0.1015
	60	334.9	(-166.3, 836.1)	0.0188	594.0	(-388.5, 1576.4)	0.0262
30	45	-73.9	(-437.4, 289.6)	0.4362	241.7	(-739.7, 1223.0)	0.3208
	60	148.2	(-274.6, 571.1)	0.1881	361.5	(-401.6, 1124.7)	0.0809
45	60	222.1	(-191.6, 635.8)	0.0480	120.0	(-848.1, 1087.8)	0.6063
T-test groups		Vitamin E					
		Difference in three month change from baseline			Difference in nine month change from baseline		
Dose	Comparison dose	Point Estimate	95% CI	p-value	Point Estimate	95% CI	p-value
0	15	0.553	(-0.947, 2.054)	0.1661	-0.878	(-2.494, 0.738)	0.0422
	30	0.770	(-0.748, 2.287)	0.0633	-0.671	(-3.201, 1.858)	0.2743
	45	0.335	(-1.055, 1.726)	0.3454	-1.320	(-3.138, 0.497)	0.0092
	60	0.413	(-1.371, 2.198)	0.3610	-1.124	(-2.984, 0.734)	0.0266
15	30	0.216	(-1.408, 1.840)	0.6156	0.207	(-2.350, 2.864)	0.7421
	45	-0.218	(-1.732, 1.295)	0.5789	-0.442	(-2.355, 1.470)	0.3345
	60	-0.140	(-1.991, 1.711)	0.7696	-0.246	(-2.208, 1.715)	0.6226
30	45	-0.434	(-1.964, 1.096)	0.2810	-0.649	(-3.259, 1.961)	0.3239
	60	-0.356	(-2.217, 1.505)	0.4631	-0.453	(-3.083, 2.177)	0.5000
45	60	0.0780	(-1.714, 1.870)	0.8621	0.196	(-1.878, 2.269)	0.7082

[1] 95% CIs are adjusted for Bonferoni adjusted p-value of 0.00125
[2] T-tests are for unequal variances
[3] Point estimate = $mean\ \Delta(comparison\ dose) - \ mean\ \Delta(dose)$



Comment [A25]: I am not a particular fan of bar charts in this setting, though they are not entirely incorrect. They just draw your attention to the difference from zero, while what we really care about is the difference from the placebo group. But this is a very minor point in this case.

Are your CI Bonferroni adjusted? I would put that in the footnote.

Figure 1: Mean Changes from Baseline in Serum Beta Carotene and Serum Vitamin E
Note: Error bars indicate 95% confidence intervals