Reviewer's report

**Title:** Vitamin E supplementation and pneumonia risk in males who initiated smoking at an early age: effect modification by body weight and dietary vitamin C

**Version:** 1  **Date:** 22 August 2008

**Reviewer:** Susan M. Graham

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Major Compulsory Revisions:
The hypothesis that vitamin E supplementation may increase pneumonia risk is certainly worth investigating. The authors have worked hard on the analysis, which has been carefully and meticulously detailed. My comments on this paper are general, but address what I see as some major flaws in this analysis. In brief, I believe their analysis needs to be redone with adjustment for important predictors of pneumonia risk before it can be considered for publication.

I have read the author's previous paper published in Chest in 2004, in which the overall finding was of no effect of vitamin E, and the subgroup finding reported was that vitamin E supplementation was associated with a 35% reduction in the risk of pneumonia among subjects who had initiated smoking at 21 years of age. The conclusion of that paper states that “the observed effects among smoking subgroups should be considered cautiously, but may warrant further investigation in the role of vitamin E in populations with high risk of community-acquired pneumonia.” I agree with the conclusion of that study regarding caution in interpretation, especially as neither the hypothesis about vitamin E and pneumonia nor the subgroup analysis were prespecified in the original trial protocol.

I am puzzled by the decision to further analyze this issue in the same dataset, rather than attempting to validate the finding in another study population, but perhaps this was not possible. It is true that a significant interaction was found between age at smoking initiation (as a continuous variable) and vitamin E supplementation group in the Chest 2004 paper. The following data are presented in that paper on the effect of vitamin E on pneumonia risk by age at smoking initiation:

# Initial age 15: RR 1.05, 0.78-1.41, n = 180
# Initial age 16-20: RR 1.17, 0.98-1.39, n = 522
# Initial age 21-24: RR 0.69, 95% CI 0.47-1.00, n = 112
# Initial age 25: RR 0.61, 0.39-0.94, n = 84
# Initial age 20: RR 1.14, 0.98-1.32, n = 701 (one case dropped?)
# Initial age 21: RR 0.65, 0.49-0.86, n = 196

These data seem to support the reported subgroup finding of that study, that
pneumonia was somewhat reduced by vitamin E supplementation among those who had initiated smoking at >21 years of age. However, it is not clear to me why this analysis focuses on the non-significant increase in relative risk among smokers who initiated at a younger age, and attempts to find evidence for a causal relationship indicating harm of vitamin E. The evidence for the increase in pneumonia risk (again, 1.14, 0.98-1.32) was weak enough in the previous analysis that this possible harm was not even commented on in the Chest publication.

More specific comments on this paper include the following:

1. The background sections in both the abstract and introduction do not adequately present the rationale for this study, nor do they clearly relate the hypothesis to the findings of the prior study and put the current paper into the context of the previous analysis.

2. The restriction of this analysis to a subset of the entire trial dataset is not clearly presented, in terms of proportion of participants and of pneumonia cases included, as well as any differences between this group and the excluded participants. It is true that a table 1 is presented in the original trial publication showing balance between the vitamin E intervention and placebo groups, but it is not clear how the men who initiated smoking earlier differed from the other men in the study, which they surely did.

3. Randomization for the ATBC study was not stratified based on age at initiation of smoking, and it is quite possible that there are some imbalances within the subgroup due to chance alone, especially with respect to important predictors of pneumonia risk. It has been recommended that “comparability of treatment groups for prognostic factors should be checked within subgroups” (please see Rothwell PM, Subgroup analysis in randomized controlled trials: importance, indications, and interpretation. Lancet 2005; 365: 176-86). I strongly feel that a table 1 should be included to examine the balance of the two groups for important predictors of pneumonia risk. In addition, both adjusted and non-adjusted results should be presented for the current analysis, including all predictors found to be significantly related to pneumonia risk in previous study. Confounding due to differences in strong predictors within this subgroup is quite possible.

4. Figures should include confidence intervals and number at risk in each group, to display the uncertainty in the data. Time-to-event plots comparing treatments by subgroups can mislead one into exaggerating the evidence of a subgroup effect.

5. In general, the paper should avoid use of terms like “harm of vitamin E” and “increased risk” definitively and be much more cautious in interpretation of the associations identified and conclusions drawn in this exploratory analysis. Post hoc observations should be treated with skepticism irrespective of their statistical significance. The authors do mention their multiple tests of interaction as a limitation, but additional caution due to the limitations I have pointed out is also warranted.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.