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2009-02-20T12:10:07Z

http://dx.doi.org/10.1016/j.freeradbiomed.2006.11.035

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Conclusions about intervention effects should not be based on surrogate end points [Letter to the Editor]

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Free Radical Biology and Medicine 2007; 42:578

Published version: **http://dx.doi.org/10.1016/j.freeradbiomed.2006.11.035**

Pre-print version of the manuscript

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Experts of controlled clinical trials argue that decisions on medical interventions should be based on clinically relevant outcomes and not on surrogates such as laboratory measurements. There are quite a few examples in which the effect on a surrogate end point substantially diverged from the effect on a clinically relevant outcome [1,2].

In this respect, the recent paper by Bruno *et al.* is problematic as it proposed higher vitamin E intakes for smokers on the basis of greater disappearance rate of α-tocopherol in the plasma of smokers [3]. The disappearance rate is a surrogate end point with no validated relation to any clinically relevant outcome.

In our analyses of the ATBC Study cohort, we found that smoking modifies the effect of 50 mg/day vitamin E supplementation; however, the modification takes place in the direction opposite to that proposed by Bruno *et al.* In the ≥72-year-old ATBC Study participants who smoked ≥15 cigarettes per day at baseline, vitamin E supplementation increased common cold incidence by 42% (95% CI: +18% to +70%), whereas in those who smoked less, vitamin E reduced common cold incidence by 29% (95% CI: −9% to −46%) [4].

Similarly, smoking modified the effect of vitamin E on pneumonia incidence. In the ATBC Study participants who had initiated smoking at later age, vitamin E reduced pneumonia incidence in those who quit smoking during the follow-up by 79% (95% CI: −40% to −93%), but had no effect on those who continued smoking (95% CI: −47% to +19%) [5].

Thus, in the case of these two respiratory infections, vitamin E supplementation appeared beneficial for those who were smoking less, but it was harmful or ineffective for those who smoked heavily at baseline or continued smoking during the follow-up. These findings with clinically relevant outcomes thus contradict the surrogate-based proposal by Bruno *et al.* that smokers would benefit of higher vitamin E intakes and it would seem necessary for them to consume at least 15 mg/day of vitamin E [3]. Furthermore, the current US RDA recommendation level for vitamin E, 15 mg/day, is not based on any clinically relevant outcome either and is arbitrary [6]. The divergence in the effects of vitamin E supplementation in the ATBC Study cohort indicates that caution should be maintained in any proposals that people should increase their consumption of vitamin E until its effects are better understood.

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