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Letter to the Editor

Conclusions about intervention effects should not be based on surrogate end points

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 from 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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