Response to comment on “Cancer chemoprevention: Evidence of a nonlinear dose response for the protective effects of resveratrol in humans and mice”

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Low-dose resveratrol did not have the opposite effect on intestinal adenoma development when given in a standard diet instead of a high-fat diet, although we agree on the need for more information on the interaction of diet-derived compounds, such as resveratrol and other lifestyle, metabolic, and hormonal factors.

The letter by Guerra et al. (1) discusses the findings reported in our recent article entitled “Cancer chemoprevention: Evidence of a nonlinear dose response for the protective effects of resveratrol in humans and mice” (2) and suggests that confounding factors may have influenced the results. They claim that “resveratrol alone had opposite outcomes on intestinal tumorigenesis in mice on standard diets; we saw no evidence of any gender-related differences in genders and resveratrol doses. Although we agree that this is possible, it is important to note that resveratrol was equally efficacious in male and female animals, and this was the case for both the high-fat and standard diets; we saw no evidence of any gender-related differences in the ability of resveratrol to protect against adenoma development.

In our article, we urged investigators to examine the effects of low, dietary-achievable doses/concentrations of candidate cancer chemopreventive agents in their experimental models. However, we did not in any way state that we expect that all compounds will display efficacy at these levels; we just consider it important to have concentrations that can be attained in human plasma/target tissues, to maximize the chances of successful translation of laboratory data to the clinic.

In their letter, Guerra et al. also provide data on the chemopreventive effects of lipoic acid (LA) in ApcMin mice. They state that “distinct antioxidants, such as LA and resveratrol, appear to have a similar linear-dose chemopreventive activity” in ApcMin mice fed equiocaloric/standard diets and imply that the compounds are acting in the same manner. However, most if not all dietary-derived compounds with anticancer activity are multitargeted and affect numerous molecular pathways; for example, at least 20 proteins have been identified as directly binding to resveratrol (3). Simply describing those with redox activity as antioxidants risks trivializing the complexity of these compounds and failing to recognize other key mechanisms of action in humans. It is likely that a variety of factors—including dose, metabolic and hormonal status, and target tissue— influence the relative contribution of different mechanisms to any cancer chemopreventive efficacy, and it represents a challenging but essential task to unravel these connections.

Last, we agree completely with the sentiments of Guerra et al. that more knowledge is needed regarding the interactions between diet-derived compounds used for cancer prevention and metabolic, hormonal, lifestyle, and environmental factors; such knowledge will come only from an improved mechanistic understanding, gained by conducting high-quality studies using clinically relevant models and clinically achievable doses.

**REFERENCES**


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