

and are less costly than randomized trials (3,4).

Lawenda et al. further discounted 10 randomized trials that we cited because of small sample size. However, only five of nine trials with concurrent radiation and five of 16 trials with chemotherapy that they cited had a sample size more than 66 patients, and five chemotherapeutic trials had a sample size of 20 or fewer patients. Although Lawenda et al. concluded that “high-dose antioxidant supplementation during radiotherapy decreases local tumor control and shortens the survival of cancer patients,” the very trials they cited do not substantiate these claims. Lawenda et al. also did not mention the survival benefit demonstrated in a 100-patient study by Lissoni et al. (Table 1), thus biasing their commentary.

Although most of the trials they cited demonstrated a decrease in side effects and several also showed an increase in treatment response and overall survival, one (5) reported an increase in disease recurrence and second primaries among smokers who received supplements. Although Lawenda et al. stated that “this study is the most important randomized clinical trial, to date, on the use of supplemental antioxidant and radiation therapy,” the conclusion drawn by the authors of that study was seriously flawed because they used retrospective capsule counts by patients to assess supplement compliance and never verified compliance by measuring antioxidant serum levels.

Lawenda et al. further stated that “anti-cancer therapies may lower plasma antioxidant concentrations by altering dietary intakes.” Although this is true, we reported that plasma antioxidants are decreased mainly by chemotherapy and radiation due to lipid peroxidation.

Lawenda et al. speculated that “antioxidants can exert their effects on all tissues to some degree, thereby protecting tumor cells as well as healthy ones.” However, the four in vitro studies they cited showed that more antioxidants accumulate in cancer cells than normal cells, which we reported (2). Accumulation of excessive antioxidants and nutrients in cancer cells can shut down oxidative reactions necessary for generating energy. Antioxidants also produce biologic effects on cancer cells unrelated to oxidative damage: they increase cancer cell

Re: Should Supplemental Antioxidant Administration Be Avoided During Chemotherapy and Radiation Therapy?

Lawenda et al. (1) expressed concerns about our review (2) of antioxidant and nutrient use during chemotherapy or radiation. The authors stated that we reviewed 52 human trials when in fact we discussed only 50. They dismissed the 36 observational studies we reviewed on the basis of study design. Unlike Lawenda et al., however, we included all pertinent peer-reviewed publications, regardless of randomization or sample size, to avoid bias and because observational studies provide valid information and virtually equivalent results as randomized trials, do not overestimate the magnitude of treatment effects,

Table 1. Trials reporting use of antioxidants with radiation therapy or chemotherapy*

Type of trial	First author (reference)†	Number of patients	Side effects decreased?	Response rate higher?	Increased survival?
Radiation	Bairati (17)	540	Yes	Not addressed	No
	Berk (42)	126	Yes	Not addressed	No difference
	Sasse (43)	1451	Yes	Yes	Not addressed
	Mell (44)	552	Yes	No difference	Not addressed
	Buentzel (45)	132	No	No difference	Not addressed
Chemotherapy	Pathak (64)	136	No difference	No difference	No difference
	Lissoni (66)	100	Yes	Yes	Yes
	Lissoni (67)	250	Yes	Yes	Yes
	Smyth (71)	151	Yes	Yes	Not addressed
	Fujimoto (74)	207	No difference	Not indicated	Yes

* Table includes all randomized trials with more than 66 patients cited by Lawenda et al.

† Reference numbers in parentheses as listed in commentary by Lawenda et al.

differentiation, apoptosis, and growth inhibition, and they inhibit or enhance gene expression and/or activity of numerous proteins. Antioxidants selectively inhibit repair of radiation damage of cancer cells but protect normal cells when antioxidants are used before, during, and after radiation, and there are no published studies showing that antioxidants protect cancer cells against radiation (6,7).

Lawenda et al. begin their commentary with the maxim “first, do no harm.” Studies involving thousands of patients have demonstrated that antioxidants and other nutrients do not interfere with chemotherapy or radiation, but instead decrease toxicity and may improve response rates and overall survival. Perhaps, then, should the first step in doing no harm be to have a discussion with cancer patients about the utility of concurrent antioxidant administration?

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