Chapter 4. Conclusions

This evidence report assessed the evidence for the efficacy of coenzyme Q10, vitamin C, and vitamin E for the prevention and/or treatment of cancer.

We identified a body of literature and were able to make the following observations from the literature's trials:

- There were no controlled trials found in the literature that presented data on the efficacy of coenzyme Q10 for prevention or treatment of cancer and therefore no conclusions, either positive or negative, can be drawn.
- There were the following results found for the use of vitamin C and vitamin E in these doses, various combinations, and populations:
- no decrease risk of death due to cancer;
- no decrease of new tumor formation for populations studied, except for one arm of the ATBC study and one tumor type (AT for prevention of prostate cancer).
- There was no decrease in risk of death for vitamin C in the doses as treatment for advanced cancer.
- There was no benefit for the development of new colonic polyps in the doses, populations tested; the combination of vitamins C and E was not clinically superior to placebo in secondary prevention and the combination of vitamins C and E with beta-carotene or vitamin A did show a trend favoring a reduction in polyp recurrence, but this finding was not statistically significant.
- There were several single trials which separately showed:
- Vitamin C was found to be beneficial in single trial bladder cancer used in conjunction with BCG for new tumors.
- Vitamin E in combination with omega-3 fatty acid increases survival.
- A number of intermediate outcomes studies were positive.
- The systematic review of the literature does not support the hypothesis that the use of supplements of vitamins C or E or coenzyme Q10 in the doses tested generally help prevent and/or treat cancer in the populations studied. There were isolated findings of benefit, which require confirmation.

Limitations of the Review

Heterogeneity

A number of issues potentially limit the effectiveness of this review. Methodologically, there was marked heterogeneity in the size of the population, the intent of the trial, the types of outcomes, and follow-up times. We identified three large primary prevention trials (ATBC, Linxian General Population and Linxian Dysplasia Group) that each reported on a number of separate outcomes. The majority of remaining trials were studies of much smaller numbers of people. They included not only secondary prevention trials but also treatment trials such as vitamin C for treatment of cancer. In addition, the populations varied from representatives of the healthy population to subjects identified at high risk for the development of cancer or who in fact

already had cancer. The observed heterogeneity in study populations and designs deterred us from conducting a meta-analysis in two of our three outcome domains—death and new tumors—and also excluded some studies from our colonic polyps analysis. In the face of this heterogeneity, we provide individual study risk ratios and discuss the studies descriptively. We cannot assess the relationship between the possible heterogeneity in treatment effects and study or population characteristics, due to the small numbers of studies available.

Quality of the Trials

Given the consistent positive effects from the observational literature, the number of clinical trials as well as their depth and quality was disappointing. The quality of these studies varied as well. More than half of the trials had a Jadad score of less than three. The presence of Jadad scores of less than three has been associated in the literature with bias.[14] In addition, we excluded from consideration case series, cohort studies and epidemiologic assessments. While these would have expanded the data base, they do not provide the most direct evidence of efficacy.

Publication Bias

We conducted a comprehensive literature search, including hand-searching reference lists of identified articles, and contacting experts. We also searched databases that include unpublished studies, such as the Cochrane registry of trials and the so-called "grey literature" (unpublished data, conference proceedings, and abstracts). Although we were unable to find any unpublished literature, we were able to include a number of conference proceedings in our analysis. Research by McAuley and colleagues[65] has demonstrated that the exclusion of the "grey literature" exaggerates the estimates of the effects of interventions that are being tested. Therefore, to the degree that there is significant unpublished or non-indexed literature pertinent to this topic that we did not find, this review is limited. Language was not an exclusion criterion for our search.

We could only test formally for publication bias in the single setting for which we did a meta-analysis, and based on only three studies. In this setting, we found no evidence of publication bias but have little statistical power given the small number of studies. We acknowledge that publication bias may still exist despite our best efforts to conduct a comprehensive search, and the lack of statistical evidence of existence.

Diverse Interventions

Clinically, a number of potential limitations could be identified as well. Few studies evaluated single agents for efficacy. There was no standard amount of either vitamins C or E given, nor were the multi-vitamin formulas consistent from study to study. Some of this variation may be due to differences in the populations assessed; however, it also reflects lack of consensus on recommended doses of these vitamins to be used therapeutically. Given the small number of studies and the differences in doses and formulas, no assessment could be made regarding effectiveness of varying dosage levels or combinations of individual supplements.

However, the ability to infer from this finding is limited because the multicomponent intervention limits our ability to attribute the reported efficacy to any particular component. However, there will always be problems of confounding variables when studies are not designed to isolate effects of single nutrients. However, take single nutrients for treating cancer, making it a challenge to test the efficacy of almost any of the treatments being used in practice.

The role of these clinical trials in understanding anti-oxidants in cancer can be expressed in a series of logical steps:

- Cellular/molecular evidence has shown that oxidation is associated with DNA and other molecular damage.
- Cellular/molecular evidence relates DNA damage to the development of cancer.
- Epidemiologic data supports a relationship between consumption of diets rich in anti-oxidants and decreased rates of cancer.
- However, the randomized controlled trials (RCTs) reviewed here failed to support the hypothesis that anti-oxidant supplements help prevent cancer.

In trying to resolve the RCT results with the cellular/molecular and the epidemiologic data there are several possible explanations:

1. The type of antioxidants used in the trials was different (synthetic vs. natural).
2. The dose used was wrong.
3. The results were due to something other than the single anti-oxidants or combinations that were tested in the trials.
4. The duration of treatment was too short.
5. The observed epidemiologic association is not causal in the same way in which the recent demonstration that epidemiologic studies relating the use of hormonal replacement therapy to potential cardiac effects in post-menopausal women was not confirmed by a definitive RCT.

The conclusion of the review is that the negative results only apply to the anti-oxidants tested, in the doses tested, and for the populations tested and do not constitute “proof” that anti-oxidants do not influence cancer. However, the generally negative results from the RCTs do place the burden of proof on the proponents of anti-oxidant supplements to identify the specific supplement, the dosage and the population combination that is efficacious.

Other Limitations

In addition, it will be difficult to generalize from this body of work, because insufficient numbers of female patients were included for study. Also, few trials were conducted on cancers specific to women, such as breast or cervical cancer. Finally, the lack of any published studies on coenzyme Q10 appropriate for inclusion in this analysis limit the ability to assess this popular therapy. Unfortunately, the only literature identified involved uncontrolled clinical trials, case series and case reports.