

What Have We Learned from Nutrition Intervention Trials on Cancers in Linxian, China?

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Background: Linxian China is a region where is one of the worlds highest rates of esophageal/ gastric cardia cancer and lacks of the micronutrients in local diet. Two randomized nutritional intervention trials were conducted from 1985 to 1991. Total 32,902 individuals of ages 40-69 was recruited in 1985 from four communes northern Linxian. Among them, 3,318 persons with esophageal dysplasia by cytology were assigned to dysplasia trial as treatment or placebo and 29,584 persons without dysplasia were assigned to general population trial according to a one-half replicate of a 24 Factorial experimental design.

Purpose of study: In this prospective study, we evaluate the long-term effect of multiple vitamin and mineral supplementation on incidence and mortality from esophageal/gastric cardia cancer as well as mortality from other diseases in Linxian for getting the references of population-based cancer intervention.

Methods: Intensive follow-up assessment of cancer incidence and cause-specific mortality was conducted from May 1985 through May 1996 for all trial participants. Endpoints were determined by monthly village doctors checks, periodic surveys, and quarterly crosscheck with County Death Reports. Statistical analysis calculated relative risks (RRs) and 95% confidence intervals (CIs) using proportional hazards models adjusted for age and sex.

Results: A total of 7,149 deaths occurred among the trial participants during the 11 years intervention period. Cancer was the leading cause (38%) of all deaths (with 75% of all cancer deaths due to esophageal/gastric cardia cancer), 27% were due to cerebrovascular disease and followed by respiratory disease (9.3%). In Dysplasia Trial: a cumulative total mortality rate was 15% lower (RR=0.85, 95%CI=0.72-1.01) among individuals of treatment vs. the placebo. Risk of total cancer was 12% lower (RR=0.88, 95%CI=0.72-1.07), esophageal cancer 19% lower (RR=0.80, 95%CI= 0.61-1.05), gastric cardia cancer 6% lower (RR=0.93, 95%CI=0.67-1.29), cerebrovascular disease 16% lower (RR=0.84, 95%=0.61-1.16) and other diseases 11% lower (RR=0.89, 95%CI=0.71-1.10).

Conclusions: Micronutrients daily supplementation may have long-term beneficial effect on reductions of mortality for total death, cancer deaths and other diseases among adults with precancerous lesions of esophagus and normal local residents in Linxian. Prevention trials with complicated factorial designs can be successfully implemented in this population. Despite multiple comparison problems, we were able to test multiple hypotheses at the same time for essentially the same cost. Lag-to-effect (mortality) impacts duration of intervention and appears to be longer than our initial assumptions allowed. The continued separation of survival curves throughout interventions suggests that benefits would be greater if interventions were longer. Some intermediate endpoints appear to be highly predictive of future cancer. In the future, smaller and shorter interventions with intermediate endpoints may be valid tests of effect. We must consider the possibility of toxicity for all agents evaluated.