

Nutritional Intervention to Prevent Hereditary Cancer

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To determine if the effect of nutritional interventions differs by genetic susceptibility to cancer, we must have both an effective intervention as well as a documented marker of genetic susceptibility. The first large clinical trials to test nutritional intervention strategies have recently been reported, and apparent efficacy has been observed for selected antioxidants in the primary prevention of several cancers, including esophageal, stomach, prostate, and colorectal cancers. At the same time, increasing numbers of markers of genetic susceptibility are being identified. Although susceptibility markers have not yet been evaluated in the context of nutritional interventions in humans, preliminary data in animals indicate that calorie restriction reduces spontaneous tumor mortality in p53-knockout mice. Linking the results from nutritional interventions in humans with markers of genetic susceptibility will allow us to better understand gene-environment interactions. [Monogr Natl Cancer Inst 17:43-47, 1995]

What evidence do we have that nutritional intervention strategies have different effects in individuals who are or are not genetically susceptible to cancer? The following two elements are necessary to answer this question: 1) We must have an effective intervention strategy, and 2) we must have a bona fide marker or markers of genetic susceptibility. At this time, there are no human cancers in which both of these elements have been documented and linked. There are, however, a number of studies that have shown a protective effect for a nutritional intervention, which should enable us to address the question when appropriate models of genetic susceptibility become available. In addition, there is at least one relevant animal model with promising results.

Prevention of Esophageal and Stomach Cancers—the Linxian General Population Trial

In the United States and Europe, the primary causes of esophageal cancer are alcohol consumption and tobacco use and, to a more limited extent, diet. In the areas of the world with the highest risk for this disease (i.e., north central China; north-eastern Iran; southern districts of Transkei, South Africa; and several Asian republics in the former U.S.S.R.), however, the causes appear to be rather different, with diet and unique exposures or practices assuming prominent roles (1). The role of host susceptibility in esophageal cancer has been little studied and is not well understood.

Some of the world's highest incidence and mortality rates for cancer of the esophagus occur in north central China, and the highest Chinese rates are found in Linxian, a rural county in Henan Province (2,3). Historically, in this area, cancers of the esophagus and gastric cardia both have been considered esophageal cancer and, thus, cannot be separated in rate calculations or retrospective analyses. The reasons for the exceptionally high cancer rates in Linxian are not known, but studies during the past 30 years have generated several hypotheses, most prominently dietary, including excessive ingestion of foods that contain factors that may increase risk (e.g., nitrosamine-contaminated fermented and moldy foods) and inadequate ingestion of foods that contain factors that may confer protection (e.g., riboflavin, retinol, carotenes, ascorbic acid, vitamin E, zinc, and molybdenum) (4-7).

Because of its extraordinarily high rates of esophageal/gastric cardia cancer and subclinical deficiencies of several micronutrients among the population, Linxian was selected for a randomized intervention trial to test whether supplementation with multiple vitamins and minerals might reduce the rates of these cancers.

From March 1986 through May 1991, 29 584 adults participated in a nutritional intervention trial in Linxian (8,9). The 40- to 69-year-old subjects were randomly assigned to intervention groups according to a one-half replicate of a 2⁴ factorial experimental design, which enabled simultaneous testing for the effects of four combinations of nutrients: 1) retinol and zinc, 2) riboflavin and niacin, 3) ascorbic acid and molybdenum, and 4) beta carotene, selenium, and α -tocopherol (Factors A, B, C, and D, respectively, in Tables 1-3). Doses ranged from one to two times the U.S. Recommended Daily Allowances (Table 1).

The intervention was successful in improving the micronutrient status of persons who received active agents to levels consistent with well-nourished Western populations, and supplemented groups had significantly better status than nonsupplemented groups (Table 2).

A total of 2127 trial participants died during the intervention period. Cancer was the leading cause of death; 32% of all deaths were due to esophageal or stomach cancer. Significantly lower

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Table 1. Daily doses and types of micronutrients by treatment factor in the general population trial in Linxian, China*

Factor	Micronutrients	Dose/day
A	Retinol	5000 IU
	Zinc	22.5 mg
B	Riboflavin	3.2 mg
	Niacin	40 mg
C	Ascorbic acid	120 mg
	Molybdenum	30 µg
D	Beta carotene	15 mg
	Selenium	50 µg
	α-Tocopherol	30 mg

*Adapted from (9).

Table 2. General population trial compliance assessed biochemically over 5-year intervention*

Biochemical assessment					
Retinol, µg/dL, plasma					
Factor†	Base line‡		During intervention		P§
	No.	Mean (SD)	No.	Mean (SD)	
A	47	35.7 (8.8)	479	54.0 (16.0)	.0001
No A	60	35.5 (13.1)	419	43.0 (14.9)	
Riboflavin (erythrocyte glutathione reductase activation coefficient)					
Factor†	Base line‡		During intervention		P§
	No.	Mean (SD)	No.	Mean (SD)	
B	56	1.73 (0.34)	747	1.19 (0.25)	.0001
No B	51	1.78 (0.40)	745	1.44 (0.31)	
Ascorbic acid, mg/dL, plasma					
Factor†	Base line‡		During intervention		P§
	No.	Mean (SD)	No.	Mean (SD)	
C	49	0.15 (0.13)	730	0.81 (0.47)	.0001
No C	49	0.25 (0.29)¶	740	0.54 (0.41)	
Beta carotene, µg/dL, plasma					
Factor†	Base line‡		During intervention		P§
	No.	Mean (SD)	No.	Mean (SD)	
D	47	5.9 (5.5)	443	85.5 (78.5)	.0001
No D	60	6.8 (5.8)	455	12.0 (15.0)	

*Adapted from (8).

†A = retinol + zinc; B = riboflavin + niacin; C = ascorbic acid + molybdenum; D = beta carotene + selenium + α-tocopherol.

‡Base-line nutritional assessment, conducted May 1985; values adjusted for season.

§P values are for t tests of factor versus not factor during intervention.

¶P value for "C" versus "No C" at base line = .03.

total mortality (relative risk [RR] = 0.91; 95% confidence interval [CI] = 0.84-0.99; P = .03) occurred among those receiving beta carotene-α-tocopherol-selenium supplementation, due

Table 3. RRs for mortality by treatment factor in the general population trial in Linxian, China*

Cause of death	No.	RR by treatment factor†			
		A	B	C	D
Total	2127	1.00	0.97	1.01	.91‡
Cancer	792	0.97	0.98	1.06	.87‡
Esophagus	360	0.93	0.90	1.05	.96
Stomach	331	1.03	1.00	1.09	.79‡
Cardia	253	1.22	1.03	1.07	.82
Noncardia	78	0.59‡	0.94	1.17	.72
Esophagus + cardia	613	1.04	0.95	1.06	.90
Other	101	0.94	1.24	0.98	.80
Cerebrovascular	523	0.99	0.93	1.04	.90
Other	812	1.04	1.00	0.94	.96

*Adapted from (9).

†A = retinol + zinc; B = riboflavin + niacin; C = ascorbic acid + molybdenum; D = beta carotene + selenium + α-tocopherol.

‡P ≤ .05.

mainly to lower cancer rates (RR = 0.87; 95% CI = 0.75-1.00) (Table 3). Site-specific mortality was reduced for cancers of the stomach (RR = 0.79; 95% CI = 0.64-0.99) and esophagus (RR = 0.96; 95% CI = 0.78-1.18). Reduced stomach cancer mortality was seen for both cardia (RR = 0.82; 95% CI = 0.64-1.04) and noncardia (RR = 0.72; 95% CI = 0.46-1.14) tumors. Mortality from noncardia stomach cancer among recipients of retinol plus zinc was also reduced (RR = 0.59; 95% CI = 0.37-0.93), based on a total of 78 cases, but this was balanced by an increase in stomach cancer in the cardia (RR = 1.22; 95% CI = 0.95-1.56; n = 253 cases), so that there was no overall benefit of treatment with retinol plus zinc on stomach cancer mortality (RR = 1.03; 95% CI = 0.83-1.28). No other significant effects on disease were found for supplementation with retinol and zinc, riboflavin and niacin, or ascorbic acid and molybdenum. Patterns of cancer incidence, based on 1298 cases, generally resembled those of cancer mortality. The findings suggest that vitamin-mineral supplementation, particularly with the combination of beta carotene, α-tocopherol, and selenium, among Linxian adults may reduce total and cancer mortality, due mainly to reductions in stomach and esophageal cancers.

Evidence for Esophageal/Gastric Cardia Cancer Genetic Susceptibility

At least three lines of evidence support the idea that there is genetic susceptibility for esophageal/gastric cardia cancer in high-risk Chinese populations: 1) an association of positive family history with increased risk, 2) evidence of familial aggregation of cases, and 3) segregation analyses suggesting mendelian inheritance in high-risk families.

Evaluation of a positive family history comes from epidemiological studies. In Linxian, China, a family history of esophageal cancer is very common: 32% of participants in the general population trial and 43% of participants in the dysplasia trial (another trial conducted in Linxian among persons at especially high risk of esophageal cancer because they had cytologic

evidence of esophageal dysplasia) reported at least one family member with a history of esophageal or stomach cancer (8). Case-control and retrospective cohort studies in these and other high-risk Chinese populations have shown a consistent association between positive family history and the occurrence of esophageal/gastric cardia cancer, with odds ratios ranging from 1.4 to 7.9 (7,10-12). During the prospective general population trial in Linxian, participants with a positive family history of cancer had a 40% increased risk of developing esophageal cancer (Table 4), and risk increased progressively with the number of affected first-degree relatives (13).

To look for familial aggregation of esophageal/gastric cardia cancer, we determined family history in households in Yangcheng, Shanxi Province, in 1979 and then identified all deaths from esophageal/gastric cardia cancer in selected villages from 1979 through 1989 (14). Only 5% of families with no history of esophageal/gastric cardia cancer in 1979 reported cases by 1989, but 19% of families with a history of esophageal/gastric cardia cancer reported new deaths from this disease over the same time period (Table 5).

Using logistic regression models, segregation analysis was performed on 221 high-risk nuclear families from Yaocun Commune, Linxian, who had at least one affected family member and all offspring older than 40 years (15). Results indicated a

mendelian pattern of transmission, most likely from an autosomal recessive gene with an estimated frequency of 19%. It was further estimated that 4% of the population is predisposed to the development of esophageal cancer as a result of such an autosomal recessive gene. Segregation analysis was also performed in another set of nuclear families from high-risk pedigrees in Shanxi Province, with results again suggesting a mendelian transmission pattern (Bonney G, Hu N, Dawsey SW, et al.: unpublished data).

Linking Intervention Results and Cancer Susceptibility

The Linxian general population trial has shown efficacy for selected antioxidants in the prevention of esophageal and stomach cancers. White blood cells were collected as a source of DNA in more than 6000 participants at the end of the Linxian studies, and other biological samples that might be suitable for DNA analyses (e.g., cytology smears and histology slides) exist on many other trial participants. The future identification of an esophageal or stomach cancer susceptibility gene(s), in combination with continued follow-up of trial participants, will allow comparison of the intervention's efficacy among persons who had or did not have the gene.

Other Intervention Studies—ATBC Cancer Prevention Study

The only other reported nutritional intervention trial large enough to have cancer end points (other than skin cancer) is the Alpha-tocopherol, Beta-carotene Lung Cancer Prevention Study (the ATBC Cancer Prevention Study) (16,17). This study was a randomized, double-blind, placebo-controlled, 2 × 2 factorial design, primary prevention trial testing the hypothesis that supplements of α -tocopherol (50 mg/day) and/or beta carotene (20 mg/day) can reduce the incidence of lung and other cancers in male smokers. From 1985 to 1993, 29 133 eligible male smokers, 50-69 years old at entry, were randomly assigned to receive active supplements or placebo capsules daily for 5-8 years (median = 6.1 years).

During the trial, 2291 new cancers were identified, including 876 lung, 250 prostate, 155 bladder, 149 colorectal, and 126 stomach cancers; 34% fewer prostate and 16% fewer colorectal cancers were observed in participants who received α -tocopherol compared with those who did not (Fig. 1). Whole blood collected from more than 20 000 participants near the end of the trial will permit research on the relationship of genetic susceptibility markers and intervention effects, both beneficial as well as harmful (e.g., the unexpected finding of increased lung cancer risk among participants given supplements of beta carotene). As examples, the MSH2 and MLH1 polymorphisms (on chromosomes 2p16 and 3p21, respectively) that have been associated with hereditary nonpolyposis colorectal cancer could be evaluated in relation to the efficacy of α -tocopherol for colorectal cancer.

Table 4. Odds ratio (OR) for esophageal cancer by family history of cancer in the general population trial cohort from Linxian, China (n = 640 cases)*

Family history of cancer	No. of cases	OR	95% CI
None	360	1.0	—
Any	279	1.4	1.1-1.8
Father	119	1.6	1.3-2.1
Mother	148	1.8	1.5-2.3
Brother	45	1.4	0.9-3.1
Sister	28	1.6	0.8-3.1
No. of first-degree relatives with cancer			
0	377	1.0	—
1	190	1.5	1.1-1.9
>1	70	1.9	1.3-2.7

*Adapted from (13).

Table 5. Shanxi Province familial aggregation study: number of families in study villages with esophageal/gastric cardia cancer deaths from 1980 through 1989 by family history*

	No. of esophageal/gastric cardia cancer deaths per family prior to 1980				
	0	1	2	3	1+
No. of families with esophageal/gastric cardia cancer deaths, 1980-1989	219	41	32	37	110
Total No. of families	4447	251	182	159	592
% families with esophageal/gastric cardia cancer deaths, 1980-1989	5	16†	18†	23†	19†

*Adapted from (14).

†P<.001 compared with families with no esophageal/gastric cardia cancer deaths prior to 1980.

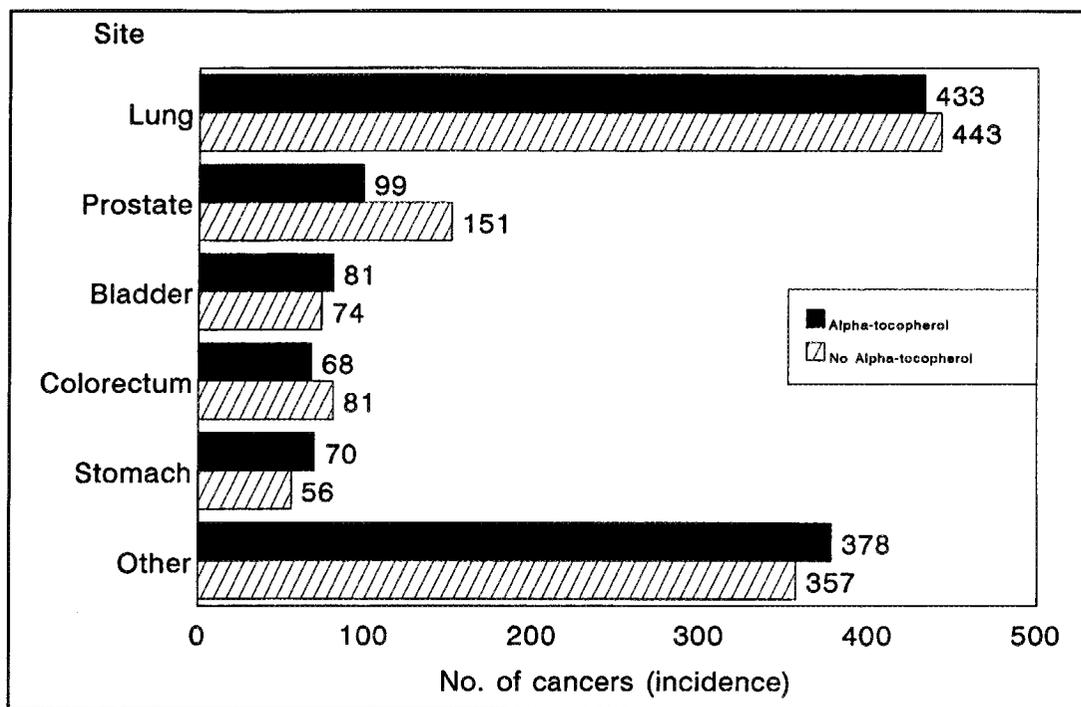


Fig. 1. Incident cancers by α -tocopherol treatment in the ATBC Cancer Prevention Study. Excludes nonmelanoma skin cancers. Adapted from (17).

Animal Models

An exciting new transgenic animal model using p53-knockout mice (in which both alleles of the p53 tumor suppressor gene are inactivated by gene targeting) has recently been used to test cancer prevention strategies. In one such study, tumor development in response to caloric restriction was evaluated (18,19). Mortality from spontaneous tumors was 100% by 28 weeks in the mice fed ad libitum, but it was only 57% in mice restricted to 60% of the ad libitum calorie level. Furthermore, multiple tumors were present in 34% of the mice fed ad libitum but in only 16% of the calorie-restricted animals by 28 weeks (Table 6). Although all the p53-knockout mice in both groups died by the end of the study (48 weeks), median survival was significantly longer in calorie-restricted animals compared with animals fed ad libitum (25 versus 16 weeks). Although results from this experiment are not directly relevant to humans, the delay in tumor onset observed in calorie-restricted mice supports the general notion that dietary manipulation can be beneficial even in the presence of strong genetic susceptibility.

Table 6. Spontaneous tumorigenicity in p53-knockout mice fed ad libitum or fed calorie-restricted diets*

Calorie group	Mortality from tumor, 28 wk, %	Multiple tumors, 28 wk, %	Mortality from tumor, 48 wk, %	Median survival, wk
Ad libitum (n = 30)	100	34	100	16
60% calorie restricted (n = 28)	57	16	100	25

*Adapted from (18,19).

Summary/Conclusion

The recent demonstration of efficacy for nutritional interventions in several large cancer prevention trials and the rapidly expanding number of molecular genetic markers offer, for the first time, the exciting and unique opportunity to examine intervention effects according to genetic susceptibility status. Preliminary data in animals suggest that nutritional intervention can be efficacious in genetically susceptible rodents. Targeting effective nutritional intervention approaches to high-risk populations identified by genetic susceptibility markers may be an important new strategy in cancer control.

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