Supplemental Antioxidant Nutrients and Cancer Prevention: What We've Learned

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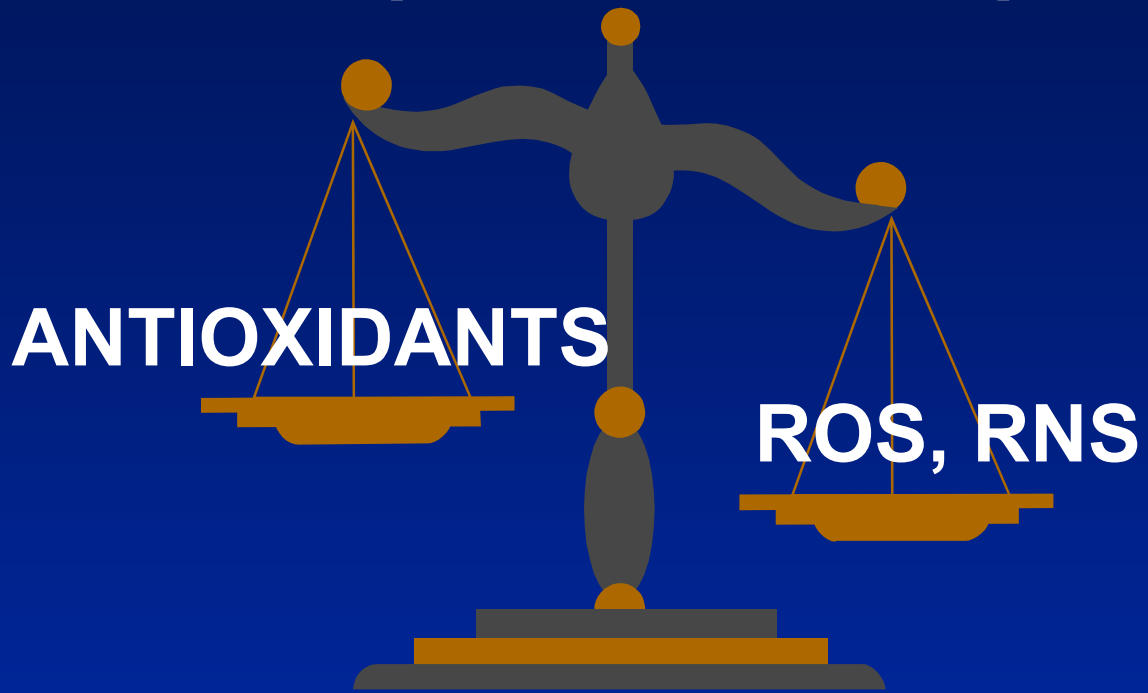
Oxidative Stress

An imbalance between oxidants and antioxidants that causes damage to DNA, proteins, and lipids



Antioxidant Defense System: Nutrients

- **Fat Soluble Vitamins**
  - Vitamin E blocks chain reaction of lipid peroxidation
  - β-carotene/carotenoids quench singlet oxygen molecules
- **Water Soluble Vitamins**
  - Vitamin C quenches a variety of ROS/RNS
- **Indirect**
  - Selenium: constituent of glutathione peroxidases which prevent generation of ROS

Role of Oxidation in Carcinogenesis

- Oxidative stress suggested to be involved in the etiology of numerous chronic diseases
- With regard to cancer, ionizing radiation produces oxygen free radicals and 8-oxodG
  - **Direct effects on DNA**
- Many classic tumor promoters produce oxygen radicals
- Inflammation produces radicals

Historical: Rationale for Trials of Supplemental Antioxidant Nutrients

- Tobacco exposure is a primary source of oxidative stress and increases risk of many malignancies
- Evidence from observational studies: increased intake of antioxidant nutrients from foods reduces risk of tobacco-related cancers

Lung Cancer Incidence by Duration Smoked & Carotene Index (*Shekelle et al., Lancet 1981)*

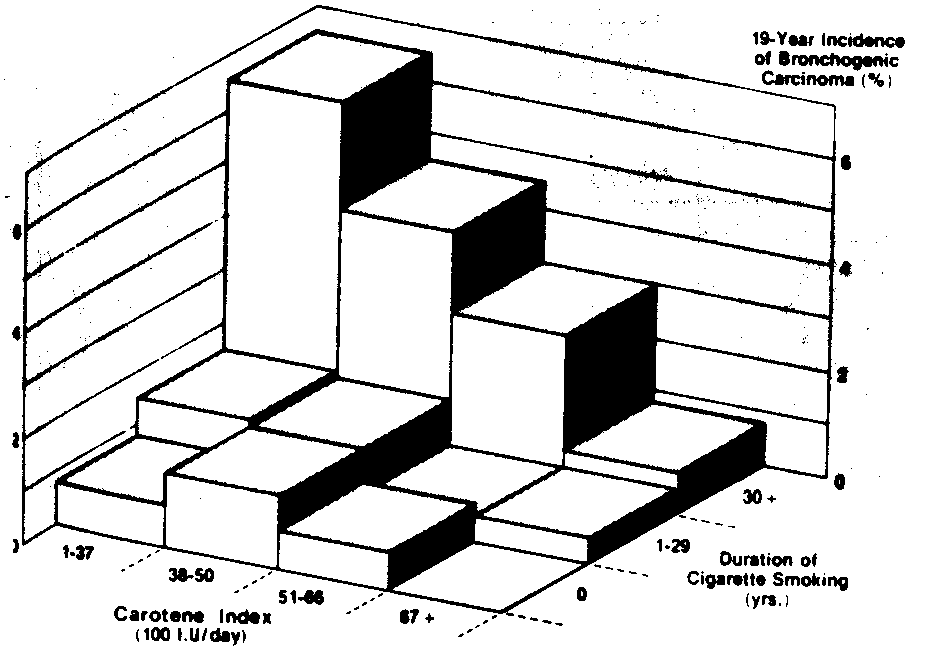


Fig. 1—Bivariate association of carotene index and duration of cigarette smoking with 19-year incidence of lung cancer.

Ratio of cases to number at risk in each quartile of carotene index, low to high, for men who reportedly had never smoked cigarettes was 1/129, 2/139, 1/149, and 0/158; for men smoking 1–29 years, 3/204, 3/218, 1/208, and 1/211; and for men smoking >30 years, 10/155, 6/132, 4/132, and 1/119.

International Agency for Research on Cancer (IARC), World Health Organization

"There is sufficient evidence for cancer-preventive activity of beta-carotene in experimental animals"

- ✓ **Mouse skin tumor models**
- ✓ **Hamster buccal pouch model**

- ⊗ **Not effective in respiratory tract models**

Source: IARC Handbooks of Cancer Prevention, Volume 2, Carotenoids, 1998.

Trials of Supplemental Beta-Carotene in Oral Premalignancy

- 6 non-randomized trials reported response rates ranging from 44% to 97%
  - (Garewal 1990; Garewal 1999; Toma 1992; Malaker 1991;Kaugars 1994; Barth 1997)
- 3 randomized/blinded trials:
  - Zaridze 1993: OR = 0.62 ($p < 0.05$)
  - Stich 1988: CR 27.5% BC+A; 14.8% BC; 3% P ($p < 0.05$)
  - Sankaranarayanan 1997: 52% A; 33% BC; 10% P ($p < 0.0001$)

(Mayne & Lippman, Principles and Practice of Oncology 6th Ed.)

Linxian County, China Cancer Prevention Trial
Blot et al., JNCI 1993

- Micronutrient deficient population from rural China (n = 29,584); high risk of gastric and esophageal cancer.
- Partial factorial design, 4 nutrient combinations evaluated.
- Primary analysis: combination of beta-carotene (15 mg/d) + vitamin E (30 mg/d) + Se (50 μg/d) reduced cancer deaths (13%), especially gastric cancer (RR = 0.79, 95% CI 0.64 - 0.99).
- Vitamin C (120 mg/d) + molybdenum, RR gastric cancer 1.09 (95% CI 0.88 - 1.36).

Linxian Cancer Prevention Trial

- Supported the concept of chemoprevention (with antioxidant nutrient supplements)
- Generalizable to well-nourished populations?

Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (*ATBC, NEJM 1994*)

- Lung cancer prevention trial in 29,133 male smokers from Finland
- Supplementation with beta-carotene (20 mg/d) or vitamin E (50 mg/d), 2 X 2 factorial design for 5-8 years
- Primary outcome: Lung cancer increased 18% in men who received supplemental beta-carotene (RR 1.18, 95% CI 1.03-1.36)
- Vitamin E no effect (RR = 0.98, 0.86-1.12)

Incident Cancers in ATBC, by Treatment Arm
Source: ATBC, JNCI 1994

β-Carotene vs. No

Lung 474 vs. 402

- **Prostate 138 vs. 112**
- **Bladder 79 vs. 76**
- **Colorectal 76 vs. 73**
- **Stomach 70 vs. 56**

Vitamin E vs. No

Prostate 99 vs. 151

- **Lung 433 vs. 443**
- **Bladder 81 vs. 74**
- **Colorectal 68 vs. 81**
- **Stomach 70 vs. 56**

Carotene and Retinol Efficacy Trial (CARET)
Omenn et al., NEJM 1996

- Primary lung cancer prevention trial, multi-center, in 18,314 smokers and asbestos workers (men and women)
- Combination intervention: beta-carotene (30 mg/d) plus retinyl palmitate (25,000 IU/d) vs. placebo
- Primary outcome: Lung cancer increased 28% in subjects who received supplemental BC + A (RR 1.28, 95% CI 1.04 - 1.57)
- Risk evident in current smokers only

Cumulative Incidence of Lung Cancer, by Treatment, CARET (*Omenn et al., NEJM 1996*)

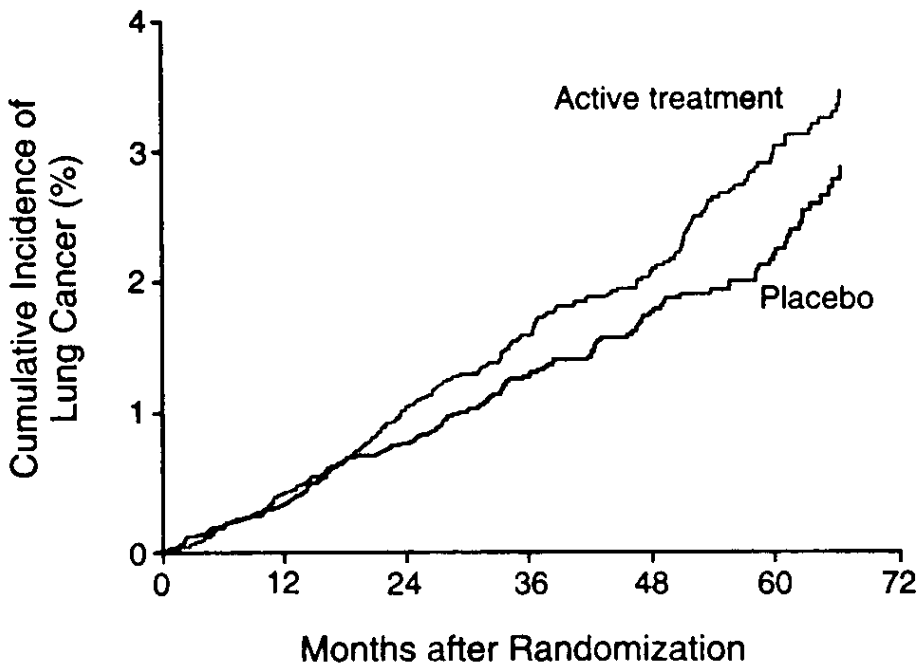


Figure 1. Kaplan–Meier Curves of the Cumulative Incidence of Lung Cancer among Participants Receiving Active Treatment and Those Receiving Placebo.

Data are shown only through 5½ years of follow-up because of the small numbers of participants beyond that time.

Physicians' Health Study I (PHS)
Hennekens et al., NEJM 1996

- Primary prevention trial of total cancers
- 22,071 male physicians randomized to beta-carotene (50 mg qod) or placebo for 12 years
- Primary outcome: total cancer RR = 0.98 (95% CI 0.91 - 1.06)
- Lung Cancer: no evidence of an increase in lung cancer risk in any smoking strata (current smokers RR = 0.90).

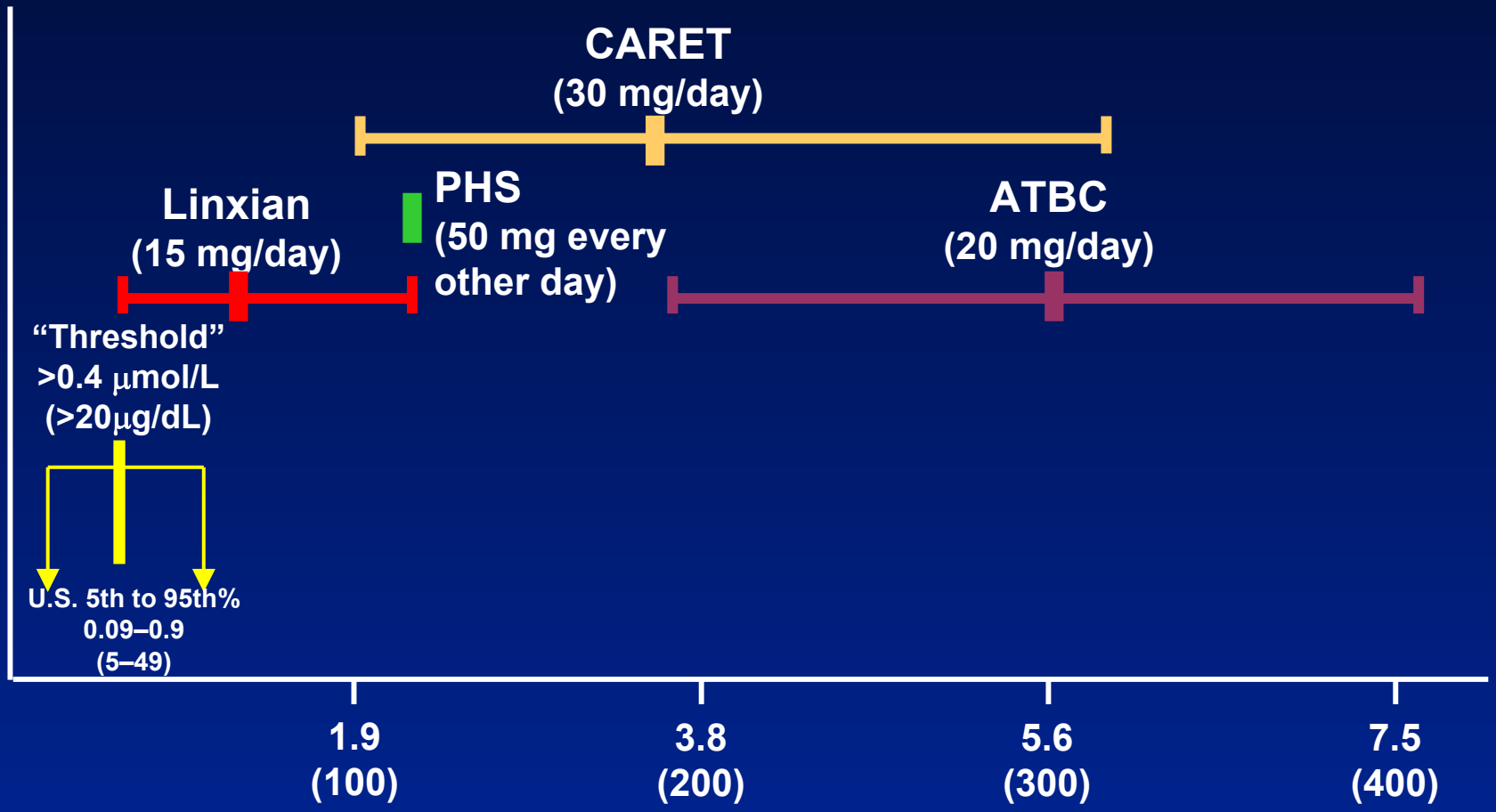
Clues from Subgroup Analyses in BC Trials: Effect of Concurrent Smoke Exposure

- CARET
  - RR = 0.80 for former smokers
  - RR = 1.42 for current smokers
- ATBC
  - RR = 0.97 for 5-19 cigarettes/day
  - RR = 1.25 for 20-29 cigarettes/day
  - RR = 1.28 for more >29 cigarettes/day
- PHS
  - RR = 0.78 for nonsmokers
  - RR = 1.00 for former smokers
  - RR = 0.90 for current smokers

"Optimal" Concentrations of Beta-carotene in Plasma/Serum (*Mayne, PPO Updates 1998*)

AUTHOR	ENDPOINT	CONC. ug/dL
Greenberg	Death	18-28
Stahelin	Total cancers	≥18
	Lung cancer	≥18
Menkes	Lung cancer	≥29
Comstock	Lung cancer	≥16
Nomura	Lung cancer	≥29
Connett	Lung cancer	≥12
Zheng	Oropharyngeal cancer	≥15
Nomura	UADT cancer	≥17

Plasma β-Carotene Concentrations in Large Population Studies



(*Mayne, PPO Updates 1998*)

Other than the Linxian trial, is there evidence of benefit for any tumor site with supplemental antioxidant nutrients?

Carotene Prevention Trial: Primary Endpoints by Treatment Arm

Endpoint	BC (n)	Placebo (n)	RR (95% CI)
Local recurrence	16	21	0.72 (0.37-1.39)
Any H & N cancer	19	25	0.69 (0.39-1.25)
Lung Cancer	13	9	1.44 (0.62-3.39)

Mayne et al., Cancer Res. 2001

RR of Regression/Progresson for Intestinal Metaplasia (*Correa et al., JNCI 2000*)

Treatment	RR Regression	RR Progression
Placebo	1.0	1.0
Anti-HP	3.1*	0.4*
Beta-carotene	3.4*	0.5
Vitamin C	3.3*	0.5
Anti-HP + BC	3.1	0.9
Anti-HP + C	4.1*	0.5
BC + C	5.4*	0.4

***p < 0.05**

Selenium Skin Cancer Prevention Trial *(Clark et al., JAMA 1996)*

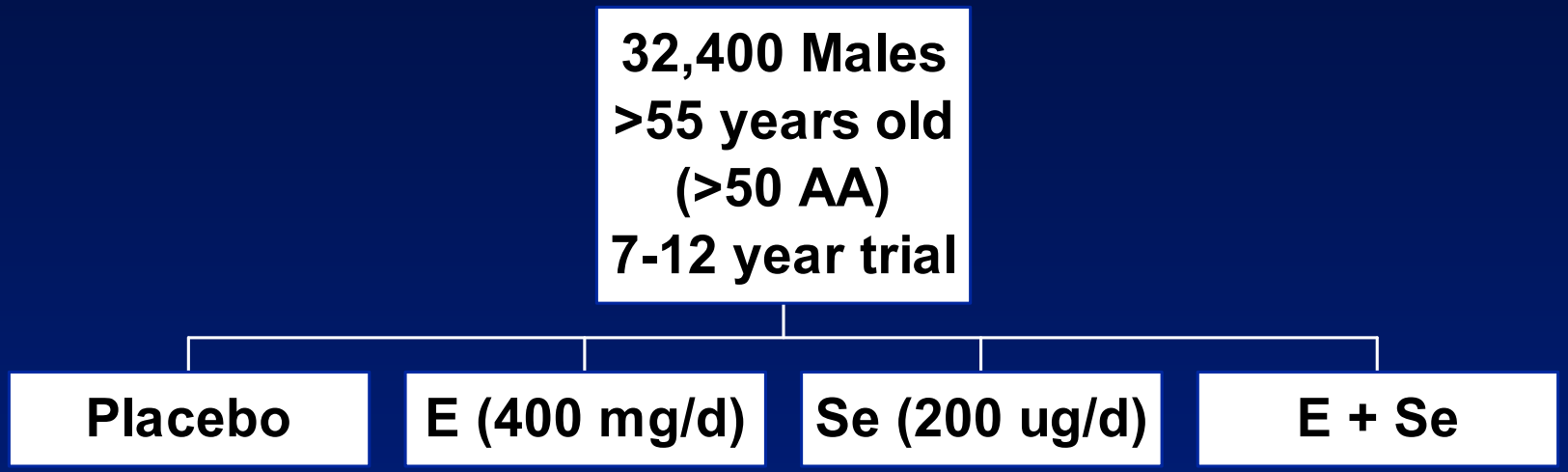
- 4.5 years of supplementation with selenium-enriched yeast (200 μg/d), n=1,312 persons with prior skin cancer from low-Se regions.
- No reduction in second skin cancers but unexpectedly noted fewer cancers of the:

Prostate:	13 Se vs. 35 P (p = 0.002)
Lung:	17 Se vs. 31 P (p = 0.04)
Colon/rectum:	8 Se vs. 19 P (p = 0.03)

Antioxidant Nutrients and Cancer Prevention

- **Beta-Carotene**
  - ↳ No clear benefit, some harm observed
- **Vitamin C**
  - ↳ Observational epi supportive but Linxian trial negative
- **Vitamin E**
  - ↳ Unexpected reduction in incident prostate cancer in ATBC Study
- **Selenium**
  - ↳ Trial data promising but based on small numbers

Selenium & Vitamin E Chemoprevention Trial (SELECT)



Primary Endpoint: Incident prostate cancer

Secondary Endpoints: Lung, colon, other cancers, deaths, CVD events

Limitations of trials like SELECT

- Enormously expensive
- Logistically difficult
- Only one dose/formulation evaluated for each nutrient
- Intervention may be too late
- Intervention may be of insufficient duration
- Lifestyle factors may modify effects

Research Needs

- Validation of intermediate endpoints of cancer risk: do they predict?
  - **Prostate intraepithelial neoplasia?**
- Development and validation of biomarkers of oxidative stress: do they predict? Need to know before using as basis for intervention
- Cohort studies and large RCTs may be extremely useful for biomarker studies

Antioxidant Nutrients and Cancer Prevention: Where are We Now?

- Many second generation “antioxidant” trials underway, based on promising results in first generation trials
- Despite some promising leads, no consistent evidence to support general use of antioxidant nutrients for cancer prevention
- Unanticipated adverse (site-specific) effects can occur
- Mechanistic understanding of role of oxidative balance in cancer limited at present


FRESH ANTIOXIDANTS
W Miller