LESSONS FROM THE RESULTS OF OBSERVATIONAL STUDIES AND TRIALS OF BETA-CAROTENE AND VITAMIN E?

Julie E. Buring, ScD

American College if Epidemiology

Chicago, September 2003

BETA-CAROTENE AND CANCER

- At the time the randomized trials began, animal and laboratory studies had showed beta-carotene could block the carcinogenic process and inhibit specific tumor growth, due to: quenching of singlet oxygen? enhanced gap junction communication? increased immunologic function?
- Large body of observational epidemiologic evidence had consistently demonstrated those with high intake of fruits and vegetables, over long periods of time, had lower risk of cancer, especially lung.

BETA-CAROTENE AND CANCER

- Believed led to beta-carotene: these fruits and vegetables were high in beta-carotene, and those with highest serum beta-carotene levels had lowest risk.
- Idea of supplementation with beta-carotene was felt to be very promising, as compliance with 5 servings per day of fruits and vegetables is low, beta-carotene appeared safe (lack of toxic effects of long-term high-dose beta-carotene in patients treated for photosensitivity diseases), and many people prefer taking a pill to changing their diet.

BETA-CAROTENE AND CANCER

- But concerns that those consuming high intakes of fruits and vegetables were systematically different than those who didn't, in ways related to cancer.
- RCT's were begun to evaluate the role of supplementation with beta-carotene in chemo-prevention of cancer.

BETA-CAROTENE AND CANCER

- Two large-scale RCT's in well-nourished populations (ATBC, CARET) showed no benefit of beta-carotene on development of lung cancer, and in fact an increased risk of lung cancer among heavy smokers given high-dose beta-carotene supplementation. A third RCT (PHS) found no benefit or harm with over 13 years of lower-dose supplementation, but low proportion of heavy smokers.

BETA-CAROTENE AND CANCER

- Lack of demonstration in the RCT's of the benefit of beta-carotene suggested by the observational studies may not have been unexpected. Could be due to many factors:
  - that there truly was uncontrolled/uncontrollable confounding in the observational studies - this, then would be the trial doing its job
  - incorrect leap to one single specific agent (fruits and vegetables $\rightarrow$ supplementation with beta-carotene) - wrong agent and/or loss of synergy with other nutrients in diet
  - too short duration of trial (3-5 years)

BETA-CAROTENE AND CANCER

- But how to explain unexpected paradoxical exacerbation of lung carcinogenesis by beta-carotene supplementation?
  - high dose of a more bioavailable form resulted in blood levels a magnitude higher than seen in the observational studies.
  - led back to basic research in animal models, which found aberrant metabolism of beta-carotene at high doses in presence of high oxidative stress (i.e., smoking). Beta-carotene may in fact act as an anticarcinogen, but its oxidized products may facilitate carcinogenesis. And other AO such as vitamin C may act as stabilizers - but vitamin C not given in the trials.

BETA-CAROTENE AND CANCER

- Further evaluation of beta-carotene supplementation is difficult: the possible co-carcinogenic properties would have to be strongly considered, especially in the context of no demonstrated evidence of benefit.

VITAMIN E AND CHD

- At the time the randomized trials began, in-vitro and animal studies had provided compelling body of evidence that oxidation of LDL and/or related oxidative mechanisms play a critical role in the initiation and progression of atherosclerosis.
- Most observational studies had shown lower risk of CHD with higher intake of vitamin E, either through food or supplements, with lowest risk seen with vitamin E intake at supplement levels. These studies conducted among healthy populations (ex. NHS), and effects seen within a short (3-5 years) duration of time.

VITAMIN E AND CHD

- The problem, however, was that it was clear that supplement users were more health conscious, and proactive in controlling other risk factors (healthy user effect) - and that these issues were "uncontrollable". RCT's were begun to evaluate role of vitamin E supplementation in prevention of CHD.
- Main RCT's completed to date have been of secondary prevention - among those with previous MI or at high risk - and have found no benefit of vitamin E on clinical CHD (GISSI, HOPE, HPT: large, well-conducted, good methodology trials).

VITAMIN E AND CHD

- Why lack of demonstration in the RCT's of the benefit of vitamin E supplementation suggested by the observational studies?
  - was supplementation with vitamin E as a single agent justified? Observational data showed greatest benefits at supplement levels, and this directly led to trial supplement design, but still focusing on one agent
  - healthy user effect; healthy complier effect; uncontrolled and uncontrollable confounding

VITAMIN E AND CHD

- secondary prevention trials: logistically logical, but the animal models had suggested effect of vitamin E on very early lesions, and did not address effect on advanced lesions. Also, participants in the trials received full treatment for CHD: led to low event rate for controls, and smaller expected benefit of vitamin E.
- correct mechanism? No measuring of oxidative stress, no assessment of effect modification by baseline oxidative stress levels.

VITAMIN E AND CHD

- What next for vitamin E supplementation and CHD?
  - Secondary prevention trials showing no effect of vitamin E for 3-5 years on advanced CHD do not answer the question raised by the animal models and observational studies (primary prevention, early development of lesions). These trials are ongoing.
  - Look at other diseases associated with oxidative stress (eg. Alzheimer's, prostate cancer).

LESSONS

- Apparent discrepancies between observational studies and trials do not mean they are necessarily contradictory or that observational studies are "wrong" - may just be looking at a different question.
- Observational studies: give best (vague) answers to real life questions, but saddled with issues of confounding.
- Trials: give precise (minimize confounding) answers, but to very specific questions which may be artificial.

- When using observational results as rationale for a trial, important to understand how the design of the trial would differ from the environment of the observational study - and most importantly, how this could impact the results, given the question you want to answer.
    - participant characteristics
    - agent characteristics
- This up-front consideration of differences and their potential impact is to allow a more intelligent use of observational data in designing trials.