β-Carotene: a Miss for Epidemiology

James R. Marshall

The report by Lee et al. (1) in this issue of the Journal makes it clearer yet that β-carotene supplements have no value as cancer chemopreventive agents. Indeed, it would now seem difficult to justify any additional investigation of β-carotene for chemoprevention. Lee et al. studied nearly 40,000 healthy women—health professionals—who were, after randomized and blinded assignment, treated for 2.1 years with placebo or a substantial experimental dose of β-carotene. The dose more than tripled the blood β-carotene levels of the experimental subjects. After treatment was halted, the subjects were followed for another 2 years. With such a limited treatment and observational duration, this study provides a weaker test than the other critical experimental studies whose results have been convincingly negative (2–4): Treatment was for only 2.1 years, and the total observation period was for only 4.1 years. However, the results of this experiment are congruent with those of the other studies (2–4)—i.e., treatment with β-carotene did not protect against cancer.

The observational epidemiologic evidence stands in sharp contrast to that generated by clinical trials—by experimental research. Epidemiologic studies have consistently shown that β-carotene is associated with a decreased cancer risk, particularly of cancer of the lung (5,6). It is the apparent consistency of the epidemiologic results in suggesting protection that makes their disjuncture with experimental results so puzzling.

It might be argued that the experimental chemoprevention trials have missed substantively important effects; this is possible but unlikely. With treatment and follow-up extending from 4 to more than 12 years, experimental studies (2–4) reveal no evidence of protective effects. There can be no arguing that the dose of β-carotene was insufficient; in each study, it more than doubled the blood β-carotene levels of the experimental subjects. Clearly, β-carotene supplements do not prevent cancer.

It might also be argued that β-carotene could be protective against cancer, even if supplementation is not. The negative association between blood levels of β-carotene and cancer risk in epidemiologic studies was observed within the range attainable by a diet containing varying quantities of foods rich in β-carotene, and it is supplementation beyond that range that imparts no protection. It is possible that, within the range of normal consumption among free-living populations, β-carotene protects, while amounts beyond that increase risk. But there is no recognized biologic reason for expecting such a curvilinear association, and there are no strong human-based data indicating the existence of one.

The most plausible explanation for the present totality of the evidence is that the conclusions that we drew from the epidemiologic evidence were wrong—wrong, perhaps, for good reasons. In case–control study after case–control study, case subjects appeared, according to indices based on their consumption of foods containing β-carotene, to have ingested lower quantities of β-carotene than control subjects had during a comparable time span. The results of prospective studies were similar: People whose reported baseline food consumption indicated that they ingested smaller amounts of β-carotene were subsequently at elevated risk of cancer. The scientific quality of the data in some of these report-based studies may have been wanting (7). However, several prospective studies based on blood samples [reviewed in (6)] indicated that individuals with lower blood β-carotene levels were more likely than those with higher blood β-carotene levels to subsequently develop cancer.

In diet report-based studies, the actual intake of nutrients is
not directly measured. Intake measures are extrapolated from subjects’ reports of usual food intake frequency and quantity. These data are coupled with nutrient density data. Although some (8) have insisted that the data generated in such studies are generally adequate for etiologic investigation, only 30%–50% of the variance observed reflects actual variance in exposure (9). Under the best of circumstances, such poor measurability would be expected to provide conservative estimates of nutrition–cancer associations; whether it consistently does so is open to question.

It is likely that many of the studies suggesting that β-carotene is protective were confounded, so that the apparent protection observed was an artifact; i.e., some correlate of β-carotene intake was actually a cause of altered cancer risk. Statistical control for confounding was not adequate. The inability to precisely measure important exposures can cause the effects of these exposures to resonate, to bias estimates of the effects of other exposures (10–12). We also understand that errors in the measurement of these exposures can be highly correlated (12,13) and that evaluating the effects of exposures in the presence of such measurement errors can be exceedingly complex. The standard statistical approaches usually used to control confounding are not sufficient (11–13).

Cancer-prevention researchers need to carefully evaluate the way consensus about the promise of β-carotene developed. The evidence seemed overwhelming. Was researcher attention so myopic that investigators published and attended to the positive studies and overlooked the null or negative ones? There are thousands of nutrients and hundreds of carotenoids in the foods that we consume. Even given the limits of present understanding, the nutrient data banks at our disposal can be used to generate indices of the intake of hundreds of nutrients. Clearly, focusing as readily as we did on β-carotene was a mistake.

Its implications were seriously incorrect with β-carotene, although there will continue to be a need in cancer-prevention research for reliance on nutritional epidemiology, i.e., on non-experimental description of the dietary experiences of free-living human beings. The number of promising nutrients and chemopreventive agents is large; to undertake randomized, controlled trials of all of them is not feasible. We need, of course, to upgrade the quality of our work (7). We especially need to better attend to imprecision and confounding in the dietary data on which much of nutritional epidemiology relies. We may need to rethink the manner in which we have mined the observational data and to recognize with greater candor the limitations and ambiguities of the epidemiologic method.

REFERENCES