Prostate cancer is an attractive and appropriate target for chemoprevention because of its incidence, prevalence, and disease-related mortality. The molecular pathogenesis of prostate cancer lends itself to a primary prevention strategy. Several histological lesions have been described, including atypical small acinar proliferation, proliferative inflammatory atrophy, and prostatic intraepithelial neoplasia. These lesions contain both genetic and

Selenium and Vitamin E: Interesting Biology and Dashed Hope

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epigenetic changes that are intermediate between normal prostatic epithelium and prostate cancer. Clinically evident prostate cancer is rare in men who are younger than 50 years, although prostatic intraepithelial neoplasia is apparent at autopsy in men who are younger than 30 years. Furthermore, the prevalence of prostatic intraepithelial neoplasia is similar in populations at much different risks of developing clinically evident cancer, indicating that external environmental influences are important and potentially modifiable. Secondary results of two randomized controlled trials, the Nutritional Prevention of Cancer study (1) and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention study (2), demonstrated substantial reduction in prostate cancer risk among patients assigned to selenium in the form of selenized yeast or vitamin E in the form of α-tocopherol, respectively, compared with risk among patients assigned to placebo. In addition, a large-scale randomized controlled trial (3) involving several different regimens found that a combination of selenium, vitamin E, and beta-carotene reduced overall cancer mortality. These clinical data, supported by epidemiological and preclinical data, led to intense interest in the potential of these antioxidant agents as a nontoxic means of preventing prostate and other cancers and notably to the Selenium and Vitamin E Cancer Prevention Trial (SELECT) (4). SELECT was designed to test the hypothesis that daily use of selenium in the form of 200 µg of l-selenomethionine or daily use of vitamin E in the form of 400 IU of all-rac-α-tocopheryl acetate, used alone or in combination, could prevent prostate cancer in more than 35,000 men at average risk.

In a randomized clinical trial reported in this issue of the Journal, Tsavachidou et al. (5) examine the intraprostatic effects of the same agents and route of administration, which were used in SELECT, in men undergoing radical prostatectomy. When given neoadjuvantly before surgery, and as assessed by a variety of measures, both selenium and vitamin E were shown to have potentially important biological effects that differentially affected specific cell types and molecular pathways and that differed further between normal epithelial, stroma, and cancer tissues. Both agents had statistically significant effects on expression levels of genes commonly associated with cancer development and progression. Selenium treatment was associated with changes in the expression of TP53, androgen receptor, HRAS, MYC, and genes involved in caspase-mediated apoptosis. Vitamin E treatment was associated with changes in the expression of TP53, HRAS, NFKB1, TGFBI, CREB1, PTEN, and AKT1. Although an integrated model of how these changes might affect the risk of developing prostate cancer was beyond the scope of the study, the study is noteworthy for demonstrating that even short-term exposure (ie, 3–6 weeks) to these agents can affect expression of a majority of the genes interrogated and, in the robust demonstration of the utility of the preprostatectomy model, for deriving information on modulation of biomarkers that may subserve the development or prevention of prostate cancer. Certainly, the findings lend credence to the previous evidence that selenium and vitamin E might be active as cancer preventatives.

Despite these interesting findings, SELECT, the largest cancer prevention trial ever performed, recently reported that neither selenium nor vitamin E in the same doses and formulations used in the Tsavachidou study had any beneficial effect on major health outcomes (6).

With a median follow-up of 5.5 years, SELECT demonstrated that neither single-agent nor combination supplementation prevented prostate cancer. Secondary analyses showed no effect on the risks of lung, colorectal, or overall cancer incidence; no effect on cardiovascular events; and no effect on overall survival. Another recently reported large-scale intervention trial, the Physicians Health II Study (PHS), also showed null results for long-term vitamin E supplementation, given orally every other day at the same dose that was used in SELECT, on both cancer and cardiovascular risks (7,8).

The negative findings of SELECT and PHS in the face of many epidemiological observations, in vivo and in vitro studies, and the study by Tsavachidou et al., all of which demonstrate convincing biological effects of these agents in various model systems and humans, are at once disappointing and puzzling. The size, operational success in terms of adherence and follow-up, and statistical power of these two large randomized controlled trials suggest that the findings of lack of benefit for selenium and vitamin E are robust and that early excitement about results of smaller trials in which prostate cancer was a secondary endpoint was overstated. Arguments that the wrong form of the agents was used in SELECT and the Tsavachidou study have been raised; however, their choices were based on expert opinion after reviewing the best available evidence at study inception (9), and given the results from SELECT, it is unlikely that large-scale trials asking similar questions for alternative formulations will be performed in the absence of more compelling scientific data. The observations that, in previous trials, those who benefited most from selenium in reducing the risk of cancer had low baseline selenium levels (1) and those who benefited from vitamin E in reducing the risk of lung cancer were primarily smokers who carry a high oxidant stress level (2) appear to suggest that the observed biological effects result in clinical benefit only in those who have an easily correctable biological deficiency. Subset analyses of these groups are underway in both SELECT and PHS, and future successes at chemoprevention are likely to rely on the identification of individuals with specific risk factors or molecular deficits that are correctable with targeted therapy. This approach is supported, for example, by studies that demonstrated interactions between antioxidant enzyme genotypes and serum nutrient levels (10). Gann has gone further by suggesting that the idea that “the protective influence of diet on prostate cancer risk—which is clearly observed in migrant studies and in populations transitioning to a Western diet—can be emulated by isolated dietary molecules given alone or in combination to middle-aged and older men” should be abandoned, reasoning that, unlike pharmacological prevention strategies [such as with finasteride, which reduced prostate cancer risk by 25% (11)], dietary prevention is more complex and “requires whole foods, extracts, or dietary patterns” (12). It may not be possible or even necessary to determine which or if an individual agent within this nutrient milieu is beneficial—dietary or nutrient supplementation prevention of cancer may be best achieved by lifelong healthy eating habits. This view is supported by an in vivo model in which a protective effect against prostate cancer

was observed for both calorie restriction and tomato powder but not for pure lycopene (13). However, the limits of even a major dietary intervention in men with early-stage low-risk prostate cancer as a secondary prevention strategy were demonstrated by a relatively modest effect on gene expression in prostate tissue (14). A final explanation of the discrepancy between observed biological effects and clinical efficacy for these agents is that contemporary model systems are too simple to accurately represent the complex biology of an intact organism. Consequently, new scientific strategies are needed.

Despite these difficulties, the prevention of prostate and other cancers remains an important public health goal. The cautionary lessons of SELECT and PHS are that well-performed large-scale controlled trials do not always validate what we believe biology indicates and that our model systems are imperfect measures of clinical outcomes in the real world.

References