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Supplements and the prostate: Widespread use, little evidence

MANY MEN TAKE VITAMINS and nutritional supplements for their perceived benefits on general health or prostate-related health, especially given the high prevalence of prostate cancer and benign prostatic hyperplasia (BPH) in men.[1–4] Of 15,387 men enrolled in the Prostate Cancer Prevention Trial,[5] 44.3% reported using a multivitamin, 35% used single supplements of vitamins C or E, and 10% to 15% used antioxidant mixtures or single supplements of vitamins A and D, zinc, or beta-carotene at least three times per week.

What should we be telling them?

On page 203 of this issue of the *Journal*, Dr. Mitchell Gaynor makes a case for the use of an isoflavone-rich diet or supplements to prevent and treat BPH, and perhaps prostate cancer, based on epidemiological and experimental evidence. Although Dr. Gaynor points out that studies are lacking, and that supplements can vary in quality, he argues there is minimal risk to the use of isoflavone supplements.

While I don't entirely disagree, Dr. Gaynor is a bit too sanguine about the utility of isoflavones in the absence of clear evidence.

Buyer beware

A concern about supplements is that their manufacture is not regulated by the US Food and Drug Administration, leading to variable quality.

For example, in a recent survey of commonly used supplements promoted for prostate health, which the investigators purchased in local stores, Feifer et al[6] reported marked variability between the supplement content listed on the label and what was found by chemical analysis. Samples of vitamin E contained from –41% to +57% of the stated dosage, selenium from –19% to +23%, vitamin D from –15% to +15%, lycopene from –38% to +143%, and saw palmetto from –97% to +140%. Of particular note: three tested samples of saw palmetto contained less than 20% of the stated dose.

Perhaps more worrisome was the recent recall of two other commonly used prostate supplements, "SPES" and "PC-SPES," because of contamination with an antidepressant and estrogen. Clearly, consumers of these supplements do not always get what they pay for.

Of additional concern is that the potential harm of nutritional supplements may not be well documented outside of a controlled clinical trial. For example, beta carotene had been thought to potentially reduce the risk of lung cancer. However, two large randomized placebo-controlled clinical trials (ATBC and CARET) found that smokers taking beta carotene actually were *more* likely to get lung cancer.

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Trials of BPH supplements needed

These observations highlight the need for well-controlled clinical trials. The agents used should have a uniform and defined content, and the trials should have appropriate statistical power and well-defined clinical end points.

Of the available agents used to treat BPH, saw palmetto (*Serenoa repens*) has been the best studied. A recent review of 21 randomized trials lasting 4 to 48 weeks (N = 3,139) concluded that, compared with placebo, *Serenoa repens* provided mild to moderate improvement in urinary symptoms and flow measures with few side effects, but its ability to prevent BPH complications such as acute urinary retention is unknown.[7]

Large-scale trials of other supplements commonly used for BPH, including isoflavones, have not been done.

ALPHA-BLOCKERS, FINASTERIDE PREVENT BPH SYMPTOMS

We do, however, have established medical therapies that can reduce or prevent BPH symptoms.

BPH consists of three entities:

- Microscopic BPH, seen histologically on prostate biopsies of men without symptoms
- Macroscopic BPH, or palpable enlargement associated with aging
- Symptomatic BPH, leading to lower urinary tract symptoms or bladder outlet obstruction.

Clinical efforts have focused on preventing symptomatic BPH. And prospective, randomized clinical trials suggest that the adverse effects on bladder function caused by BPH may be preventable.

In the Proscar Long-term Efficacy and Safety Study (PLESS)[8] in more than 3,000 men with symptomatic BPH, long-term use of finasteride reduced the risk of both acute urinary retention and the need for surgical intervention in men with moderately severe symptoms.

Recent data from the Medical Therapy of Prostatic Symptoms (MTOPS) study[9] further demonstrate that early initiation of therapy with alpha-blockers and finasteride can reduce these risks.

CAN WE PREVENT PROSTATE CANCER?

The issue of nutritional supplementation in the prevention of prostate cancer has assumed prominence in the last few years.

Between 1990 and 1997, overall cancer mortality declined, and prostate cancer mortality declined by approximately 6%.[4] The mortality rate for prostate cancer in white men in the United States is now lower than it was before the introduction of prostate-specific antigen screening in 1987.[10]

These improvements in mortality have been variously ascribed to screening, improvements in therapy, earlier and more aggressive therapy, and more appropriate application of hormone manipulation.

However, marked disparities remain in prostate cancer incidence and mortality among various ethnic groups in the United States and around the world, highlighting the relatively poor state of knowledge regarding genetic, environmental, nutritional, and biologic variables important to this disease. Furthermore, despite these advances, most men who develop metastatic disease are still destined to die of prostate cancer.

An ideal method to reduce the mortality and morbidity of prostate cancer would be through primary prevention, either through a reduction in the number of life-threatening, clinically evident cases or through a reduced age-dependent rate of development so that tumors would become evident later in life.

Trials under way

The Prostate Cancer Prevention Trial. Recognition that the androgenic milieu of the prostate is important in the development of prostate cancer led to the first wide-scale effort at prostate cancer prevention, the Prostate Cancer Prevention Trial (PCPT, SWOG-9217) with finasteride.

We have much to learn about what causes prostate cancer

Finasteride is a testosterone analogue that competitively inhibits the enzyme 5-alpha reductase (type 2) that converts testosterone to dihydrotestosterone (DHT) in the prostate, causing a profound reduction in circulating and cellular DHT. Finasteride inhibits growth of prostate cancer cells in vitro and prevents prostate cancer in certain animal models.

The PCPT is an ongoing, phase 3, double-blind, placebo-controlled, randomized trial to determine the efficacy of finasteride in preventing prostate cancer. In addition, it will yield a wealth of information on the effectiveness of prostate-specific antigen screening and on the natural history of BPH.

This trial opened in 1993 and easily exceeded the accrual goal of 18,000 men. Participants in the PCPT are currently undergoing end-of-study prostate biopsies, and results are expected in 2004.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT), a second large-scale prostate cancer prevention trial, will test the hypothesis that selenium or vitamin E

alone or in combination may prevent prostate cancer.

SELECT is based on observations in two other large-scale trials in which the incidence of prostate cancer was a secondary end point.

Clark et al[11] randomized 1,312 subjects with a history of skin cancer to receive 200 µg/day of elemental selenium in the form of selenized yeast or placebo and followed them for an average of 4.5 years for the development of basal or squamous cell carcinoma of the skin and other cancers.

While no difference was noted in rates of skin cancer, further analysis found that prostate cancer incidence was reduced by two thirds in the selenium group. Based on a small number of cases, additional stratified analyses suggested a greater reduction in prostate cancer in those with low baseline selenium blood levels, those younger than 65 years, and those with low serum prostate-specific antigen values.

The ATBC study[12] was a randomized, double-blind, placebo-controlled trial of alpha-tocopherol (50 mg synthetic *dl*-alpha-tocopheryl acetate daily) and beta-carotene (20 mg daily) alone or in combination in 29,133 male smokers aged 50 to 69. The incidence of prostate cancer was reduced 32% in those taking alpha-tocopherol.

SELECT opened in July 2001 and is projected to run until 2013. It has already reached 50% of expected accrual (> 16,200 of a planned 32,400 men) in its first year. Subjects are randomized to receive one of four treatments: vitamin E plus selenium, vitamin E plus placebo, selenium plus placebo, or placebo plus placebo. End points are prostate cancer, other cancers, or death.

Finasteride, selenium, and vitamin E are undergoing cancer trials

ADVICE TO PATIENTS

What is the best practical advice for patients regarding nutritional supplements and prostate disease?

Microscopic and macroscopic BPH appear to be normal processes of aging, and there is no way currently to predict who may go on to develop symptomatic BPH. Furthermore, there is no direct evidence that any supplement or diet actually promotes prostate "health" (or even consensus about what prostate health really is), as is commonly claimed in advertisements. Furthermore, until the results of the PCPT, SELECT, and other trials are known, no recommendation can be made regarding the efficacy of any agent in preventing prostate cancer.

A practical approach is to inform patients that:

- Some men with symptomatic BPH do report subjective improvement in voiding symptoms with a variety of supplements
- The risks of long-term supplement use are unknown
- They may not always get what they pay for
- If they are serious about preventing cancer, they should join a clinical trial.

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