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## Phase-II Study of Pomegranate Juice for Men with Prostate Cancer and Increasing PSA

Pantuck AJ, Lepper JT, Zomorodian N, et al.: **Phase-II study of pomegranate juice for men with rising PSA following surgery or radiation for prostate cancer.** *Presented at American Urological Association Annual Meeting.* San Antonio: May 22–25, 2005.

**Rating:** • Of importance.

**Introduction:** There have been a number of reports recently on the preclinical, in vitro, and in vivo anti-proliferative and apoptotic activities of pomegranate polyphenols in prostate cancer, including demonstration of a dose-dependent inhibition of cell growth/cell viability and induction of apoptosis in human prostate cancer PC3 cells associated with induction of Bax and Bak (proapoptotic); downregulation of Bcl-X(L) and Bcl-2 (antiapoptotic); induction of WAF1/p21 and KIP1/p27; a decrease in cyclins D1, D2, and E; and a decrease in cyclin-dependent kinase (cdk) 2, cdk4, and cdk6 expression [1].

**Aims:** To determine the clinical and laboratory effects of pomegranate juice on patients with prostate cancer.

**Methods:** An open-label, single-arm, 2-year, phase-2, Simon two-stage clinical trial for men with increasing prostate-specific antigen (PSA) after surgery or radiotherapy was performed. Eligible patients had a detectable PSA greater than 0.2 ng/mL and less than 5 ng/mL that was documented as increasing, enough pre-treatment PSA time points to calculate a baseline PSA doubling time, no hormonal therapy prior to entering the study, no evidence of metastatic disease, and a Gleason score of 7 or less. Patients were treated with 8 oz of pomegranate juice by mouth daily until meeting disease progression endpoints. Patients were followed in 3-month intervals for serum PSA and blood and urine were collected for laboratory studies.

**Results:** The study was fully accrued after efficacy criteria were met. There were no serious adverse events reported. None of the patients developed metastatic disease on study. Mean PSA doubling time significantly increased with treatment, from a mean of 15 to 37 months ( $P < 0.048$ ). In vitro assays using pre- and post-treatment patient serum on the growth of LNCaP showed a 12% decrease in cell proliferation and a 17% increase in apoptosis ( $P = 0.0048$  and  $0.0004$ , respectively).

### Editor's comments

Epidemiologic studies suggest that a reduced risk of cancer is associated with the consumption of a phytochemical-rich diet that includes fruits and vegetables. Fresh and processed fruits and food products contain high levels of a diverse range of phytochemicals of which polyphenols make up a large proportion. A number of phytochemicals, including resveratrol from grapes and red wine, sulforaphane from broccoli and other cruciferous vegetables, organosulfides from garlic and other allium species, limonene and perillyl alcohol from the lipid fraction of citrus peels, isoflavones such as genistein and daidzein and enterodiols from soy and flax proteins, catechins from green tea, and lycopene from tomatoes have been proposed as potential chemoprevention agents based on animal and laboratory evidence of antitumor effects. Suggested mechanisms of anticancer effects (in addition to their role as potent antioxidants) of polyphenols include the following: 1) the inhibition of human cancer cell growth by interfering with growth factor receptor signaling and cell cycle progression; 2) promotion of cellular differentiation; 3) the induction of hepatic xenobiotic enzyme activities that may provide additional defense mechanisms against oxidant stress and carcinogens; 4) inhibition of cholesterologenesis; 5) modulation of phosphodiesterase and cyclooxygenase pathways; 6) inhibition of protein kinases involved in cell signaling; and 7) inhibition of inflammation.

Although it remains controversial whether modulation of PSA levels represents a valid clinical endpoint for prostate cancer clinical trials, PSA doubling time is being seen increasingly as an important surrogate biomarker for prostate cancer mortality [2]. This study, the first clinical trial of pomegranate juice for patients with prostate cancer, demonstrated beneficial effects on PSA parameters, coupled with corresponding laboratory effects on prostate cancer in vitro cell growth and apoptosis. These results, although intriguing, require confirmation with a randomized, placebo-controlled study.

### References

1. Malik A, Afaq F, Sarfaraz S, et al.: **Pomegranate fruit juice for chemoprevention and chemotherapy of prostate cancer.** *Proc Natl Acad Sci U S A* 2005, **102**:14813–14818.
2. D'Amico AV, Moul JW, Carroll PR, et al.: **Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy.** *J Natl Cancer Inst* 2003, **95**:1376–1383.