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REVIEW

# A review of pomegranate in prostate cancer

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**BACKGROUND:** Preclinical studies showing that pomegranate juice and its components inhibit prostate cancer led to multiple clinical trials to determine whether pomegranate products could slow the growth of prostate cancer. This review summarizes the preclinical data and discusses the results of the clinical trials.
**METHODS:** Trials targeted patients on active surveillance, neoadjuvant patients, patients with biochemical recurrence (BCR) following local therapy for prostate cancer, and patients with metastatic castration-resistant prostate cancer (mCRPC).
**RESULTS:** In the BCR patient population, early phase II trials of both pomegranate juice and extract showed significant lengthening of PSA doubling time (PSADT), and confirmed the safety of pomegranate products. While a placebo-controlled phase III trial determined that pomegranate extract did not significantly prolong PSADT in BCR patients, a preplanned subset analysis of patients with the manganese superoxide dismutase (MnSOD) AA genotype showed greater PSADT lengthening on the pomegranate extract arm. In the neoadjuvant population, a large trial demonstrated a significant increase in urolithin A and a non-significant reduction in 8-hydroxy-2-deoxyguanosine, a marker of oxidation in prostate cancer tissue, on the pomegranate arm vs the placebo arm. In addition, a randomized clinical trial of a polyphenol-rich multicomponent food supplement that included a 31.25% pomegranate extract found significant slowing of PSA increase in the food supplement arm vs placebo in men on active surveillance and those experiencing BCR.
**CONCLUSIONS:** Pomegranate juice and extract are safe but did not significantly improve outcomes in BCR patients in a large placebo-controlled trial. However a subset of BCR patients with the MnSOD AA genotype appear to respond positively to the antioxidant effects of pomegranate treatment. Phase II trials of 100% pomegranate products in neoadjuvant patients and patients with mCRPC were negative. A multicomponent food supplement showed promising results in a phase II study in active surveillance and BCR patients.

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## BACKGROUND

Pomegranate products have been tested in prostate cancer patients in six phase II clinical trials[1–6] and one phase III trial[7] over the past decade, with outcomes measured by changes in PSA doubling time (PSADT), in PSA levels, and in 8-hydroxy-2-deoxyguanosine (8-OHdG), a marker of oxidation in prostate cancer tissue. The first trial, published in 2006, showed promising increases in PSADT for prostate cancer patients with recurrent disease,[3] leading to additional trials to more fully understand the role of pomegranate products in prostate cancer patients. This review summarizes the results of those trials, and offers suggestions for next steps in determining the appropriate role of pomegranate products for prostate cancer patients.

Spending on dietary supplements exceeded $36 billion in the USA in 2014.[8] More than 50% of Americans who use dietary supplements say they started taking new dietary supplements after being given a diagnosis of cancer,[9] and 58% of dietary supplement consumers report they do so to prevent or treat cancer (http://globenewswire.com/news-release/2015/04/23/727513/10130416/en/Dietary-Supplements-Market-is-Expected-to-Reach-US-179-8-Billion-Globally-in-2020-Persistence-Market-Research.html). A Canadian study reported that nearly 40% of recently diagnosed prostate cancer patients used complementary medical products, primarily to boost the immune system and to prevent recurrence.[10] The National Cancer Institute website lists pomegranate juice and extract as one of the nine dietary supplements commonly consumed by prostate cancer patients (others are calcium, soy, vitamin D, vitamin E, green tea, selenium, lycopene and modified citrus pectin).[11]

## PRECLINICAL STUDIES AND MECHANISMS OF ACTION

The first preclinical study of pomegranate products in prostate cancer, by Gil *et al.*[12] in 2000, measured Trolox equivalent antioxidant capacity of four preparations of pomegranate juice, all containing punicalagin, and anthocyanins and ellagic-acid derivatives, and reported that the polyphenols in commercial pomegranate juice had three times the antioxidant activity of green tea and red wine, both of which had shown promising antiproliferative activity in preclinical prostate cancer models.[13,14] Gil *et al.*[12] also reported that pomegranate juice contains anthocyanins, ellagic-acid derivatives and hydrolysable tannins such as punicalagins with 90% of the antioxidant activity provided by the punicalagins and other hydrolysable tannins. The same year, the Aviram *et al.*[15,16] team at the Technion in Israel reported that daily pomegranate juice consumption in healthy men and in atherosclerotic mice exerted potent, dose-dependent, antioxidant capacity against lipid peroxidation, potentially a link for the anti-atherogenic effect of pomegranate on lipoprotein, macrophage and platelets. In 2002, Kim *et al.* studied the potential antiproliferative effects of polyphenols derived from fresh

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pomegranate juice, fermented juice, aqueous pericarp extract and seed oil for breast cancer. They reported that pomegranate polyphenols can inhibit aromatase activity and decrease the endogenous synthesis of estrogen; polyphenols from fermented juice and whole-seed oil showed much greater activity than fresh juice.[17] Two earlier studies had reported that pomegranate juice contains anthocyanins, other flavonoids and phenolic acids,[18] and pomegranate pericarp contains tannins and ellagitannins.[19] Commercial juice is produced by pressing whole fruits, so the polyphenols of the fruit juice are enriched by ellagitannins[17] of the pericarp. Researchers had already found that cancer cell growth was inhibited, both *in vitro* and *in vivo*, by flavonoids[20] and tannins.[21]

On the basis of the growing body of preclinical evidence about the antiproliferative activity of the active components of pomegranate juice, a phase II clinical trial of pomegranate juice in prostate cancer patients experiencing biochemical recurrence (BCR) following definitive local therapy was launched in 2003. Results of that first trial were published in 2006 (ref. 3) and are described, along with results from six other clinical trials of pomegranate in prostate cancer, in the next section. Although no data had yet been published on the effect of pomegranate products in prostate cancer when the trial was launched, the following year Albrecht *et al.*[22] found that pomegranate extracts from fermented juice, pericarp and oil from seeds, to varying degrees, induced cell death in LNCaP, PC3 and DU 145 prostate cancer cell lines, and significantly inhibited tumor growth in nude mice through subcutaneous administration of pomegranate extract prior to PC3 xenograft tumor implantation.

Additional preclinical justification for human trials of pomegranate in prostate cancer was provided in 2005 when Malik *et al.*[23] found that an extract made from pomegranate juice, containing anthocyanins and ellagitannins, had antiproliferative and pro-apoptotic effects that are produced through modulation of cyclin-dependent kinase in PC3 cells. In 2006, the Malik Laboratory reported that the pomegranate extract used in the previous study upregulated p21 and p27 possibly blocking G1–S phase transition and causing G1-phase arrest and apoptosis. The authors also reported that pomegranate extract upregulated proteins associated with apoptosis, such as cleaved poly (ADP-ribose) polymerase and B-cell lymphoma-2-associated X protein, in PC3 cells, and downregulated proteins that block apoptosis, such as B-cell lymphoma 2.[24]

Two years later Pantuck *et al.* demonstrated that powdered pomegranate extract (POM Wonderful, Los Angeles, CA, USA), made from fruit residue after pressing for juice, has an inhibitory effect on the nuclear factor-kappaB inflammatory pathway and that such inhibition is essential for the extract to have maximum pro-apoptotic effect. In a mouse model pomegranate extract delayed the regrowth of LAPC4 androgen-independent xenograft tumors after castration and nullified the increased nuclear factor-kappaB activity that takes place during the transition from androgen dependence to androgen independence in LAPC4 xenograft tumors.[25] Nuclear factor-kappaB has been shown to be an important predictor of BCR following local therapy in prostate cancer patients.[26,27] More recently Wang *et al.* provided evidence that pomegranate extract may be effective in treating metastatic castration-resistant prostate cancer (CRPC). Pomegranate extract alone inhibited survivin and reduced the growth of C2-4 tumor cells in skeletal metastases in athymic nude mice, and enhanced the efficacy of docetaxel in mice bearing intratibial C4-2 xenografts, both by reducing serum PSA and by improving bone architecture, as compared with docetaxel alone.[28]

Results from these preclinical studies showing extensive antioxidant and antiproliferative activity of pomegranate products resulted in the launch of 10 clinical trials in prostate cancer patients.

## CLINICAL TRIALS

Trials were identified through a search, using the term 'pomegranate prostate,' in clinicaltrials.gov supplemented by searches using the term 'pomegranate prostate trial' in PubMed.gov, the European Union Clinical Trials Register and the World Health Organization International Clinical Trials Registry Platform, the Cochrane Library and the Web of Knowledge, from inception to 10 July 2016. Three trials were excluded for different reasons. A trial of powdered pomegranate extract (Venture Sciences, Noblesville, IN, USA) in neoadjuvant patients (NCT01100866), was closed due to slow accrual, and another trial of powdered pomegranate extract (POM Wonderful) in patients undergoing active surveillance (AS) (NCT02095145) is ongoing. A third trial of pomegranate juice in BPH and prostate cancer patients that measured metabolites of ellagic acid in prostate tissue in men consuming walnuts or pomegranate juice[29] was excluded because it reported no data specific to four prostate cancer patients consuming pomegranate juice.

The seven remaining trials, shown in Table 1, included trials varied in intervention (juice, powdered extract or liquid extract), length of pomegranate administration (3 weeks to 33 months) and prostate cancer patient population (neoadjuvant, biochemically recurrent and castration resistant). Four of the trials tested 100% pomegranate products. The other trials tested a 27.5% pomegranate juice blend (Biotta, Tagerwilen, Switzerland), a powdered extract combining equal amounts of active compounds from pomegranate, green tea, broccoli and turmeric (Helsinn Healthcare, Lugano, Switzerland), and a combination of pomegranate and grape juice (Tine, Oslo, Norway) with tomato products. All interventions were safe; no serious adverse events related to the study drugs were reported in any of the trials.

### Biochemically recurrent prostate cancer trials

Among men treated with prostatectomy or radiation therapy for localized prostate cancer, the state of an increasing PSA level is known as BCR. Three of the seven clinical trials of pomegranate products targeted BCR prostate cancer patients, and two other trials targeted BCR, patients along with men on AS or along with men whose disease had become castration resistant. Men with BCR often face years of uncertainty before metastatic disease becomes evident, during which time their treatment choices are usually observation or hormonal therapy. Many of these men seek alternatives to hormonal therapy to avoid its side effects. Pantuck launched the first trial of pomegranate juice in prostate cancer, targeting men with BCR, and reported results in 2006. The single arm, phase II trial enrolled 48 men (46 evaluable) who had BCR prostate cancer. Each participant received eight ounces of pomegranate juice daily until progression; 85% of the population completed 33 months on trial. The authors reported that PSADT rose from a mean of 15 months (±11 months) at baseline to a mean of 54 months (±102 months, $P < 0.001$) on treatment (with a two-fold increase in median PSADT from 11.8 to 24 months, $P = 0.029$).[3] Updated results from this study were later presented with longer-term follow-up showing durability to the PSADT change in the entire population, with the mean of 15 months at baseline increasing to 60 months post treatment ($P < 0.001$), while the median PSA slope decreased 60% from 0.06 to 0.024 ($P < 0.001$).[31] Thirteen years later, 10% of the original cohort remains on continuous treatment, having not met protocol-defined PSA progression criteria.

In 2013 Paller *et al.*[2,32] and Carducci *et al.*[1] published results of a trial of two doses of a powdered extract of pomegranate polyphenols in men with BCR prostate cancer. The trial randomized 92 patients to 1 (47) or 3 g (45) of powdered extract daily for up to 18 months. Overall median PSADT increased from 11.9 to 18.5 months ($P < 0.001$) and no dose effect was seen ($P = 0.554$). Median PSADT increased from 11.9 to 18.8 months in

**Table 1.** Summary of findings: clinical trials of pomegranate products in prostate cancer

| *Study/NCT* | *Target population* | N | *Intervention* | *Dose* | *Mean duration* | *Design* (n) | *Results* |
|---|---|---|---|---|---|---|---|
| *Juice and liquid extract trials* | | | | | | | |
| Pantuck *et al.*[3] NCT00060086 Sponsor: POM Wonderful | BCR | 42 | Pomegranate juice | 8 oz per day (570 mg per day GAE) | 33 months | Open, uncontrolled | Mean PSADT increased from 15.6 to 54.7 months ($P=001$). No serious AEs. |
| Stenner-Liewen *et al.*[5] (European trial, no NCT#) Sponsor: Biotta | CRPC 65%, BCR 35% | 97 | Juice blend of 27.5% pomegranate plus pear puree, white tea, agave concentrate, aronia berry juice | 500 ml per day (1147 mg per day GAE) | 4 weeks | Pomegranate and other juice blend (48) vs juice blend without pomegranate (49) | No difference between groups on PSA progression (38% treatment, 41% placebo, $P=0.83$); no difference in pain scores ($P=0.49$). No serious AEs. |
| Pantuck *et al.*[7] NCT00336934 Sponsor: POM Wonderful | BCR | 183 | Liquid pomegranate extract and standard juice | 8 oz per day (776 mg per day GAE[30]) | 10 months | Liquid extract (102), standard juice (17) vs placebo (64) | Median PSADT increased from baseline for each group: placebo 4.5 months, liquid extract 1.6 months, juice 7.6 months. No significant change between groups ($P>0.05$); larger increase in median PSADT change in MnSOD AA subgroup on liquid extract arm (12 months, $P=0.03$) vs on placebo 1.8 months ($P=0.22$), $P$ for difference between arms not reported). No serious drug-related AEs. |
| Paur *et al.*[4] NCT00433797 Sponsor: Throne Holst Foundation, RCN, NCS | Neoadjuvant (prior to radiation or prostatectomy) | 75 | Tomato or tomato plus pomegranate/grape juice and green and black teas | 330 ml per day of pomegranate juice in tomato+ group | 3 weeks | Tomato (26) vs tomato plus pomegranate (25) vs placebo (24) | Non-significant reduction in change in PSA for tomato plus pomegranate group vs placebo (0.28 vs 0.45 ng $ml^{-1}$, $P=0.094$). No serious AEs. |
| *Powdered extract trials* | | | | | | | |
| Paller *et al.*[2] NCT01220817 Sponsor: POM Wonderful | BCR | 92 | Powdered pomegranate extract | 1000 vs 3000 mg per day (755–2265 mg per day GAE[30]) | 13.8 months | Low dose (45) vs high dose (47) | Significant lengthening of median PSADT in the treatment group 11.9–18.5 months ($P=0.001$) no dose effect ($P=0.92$). No serious AEs; high dose showed greater incidence of diarrhea (14% vs 8%) |
| Thomas *et al.*[6] (European trial, no NCT#) Sponsor: The Primrose Oncology Fund | AS 60% BCR 40% | 199 | Capsule containing 100 mg each of pomegranate, broccoli and turmeric, and 20 mg of green tea extract | 300 mg pomegranate extract per day (GAE not reported) | 6 months | Pill (134) vs placebo (65) | AS: significantly lower PSA rise in treatment arm vs placebo (–0.1% vs 47.0%, $P=0.001$);. BCR: significantly lower PSA rise in treatment arm vs placebo (8.8% vs 80.3%, $P=0.001$). No serious AEs. |
| Freedland *et al.*[1] NCT00719030 Sponsor: POM Wonderful | Neoadjuvant (prior to prostatectomy) | 69 | Powdered pomegranate extract | 1000 mg per day (600 mg per day GAE) | 4 weeks | Extract (36) vs placebo (33) | Significant increase in urolithin A detection (34–64%, $P=0.031$) and non-significant 16% reduction ($P=0.095$) in 8-OHdG in the treatment arm. No serious AEs. |

Abbreviations: 8-OHdG, 8-hydroxy-2-deoxyguanosine; AE, adverse events; AS, active surveillance: observation only, no local treatment planned; BCR, biochemically recurrent prostate cancer, for example, men experiencing rising PSA following definitive local therapy; CRPC, castration-resistant prostate cancer; GAE, gallic acid equivalents (polyphenols); MnSOD AA, manganese superoxide dismutase AA genotype; NCS, The Norwegian Cancer Society; PSADT, PSA doubling time; RCN, The Research Council of Norway.

the low-dose arm and from 12.2 to 17.5 months in the high-dose arm.[2] In this dose exploring trial, we expected to see a greater increase in median PSADT differences from baseline to post treatment in the high-dose arm compared to the low-dose arm. The absence of such dose effects may mean that pomegranate extract is ineffective or it may mean that a large dose of extract is not more effective than a small dose. The 2006 Pantuck *et al.*[3] study reported much larger PSADT differences than the Paller *et al.*[2,32] study. Such differences could be explained by differences in the patient population, as Pantuck limited eligibility to patients with PSA $< 5$ ng ml$^{-1}$, while 32% of patients in the Paller trial had baseline PSA levels $> 5$ ng ml$^{-1}$, ranging up to 32 ng ml$^{-1}$, indicating a patient population with more advanced disease that may be less responsive to pomegranate products. However, Pantuck reported PSADT differences as means, while Paller reported PSADT differences as medians; thus no direct comparisons can be made. In addition, both the Paller *et al.*[2,32] and Pantuck *et al.*[3] studies suffered from lack of a placebo arm.

Two additional studies of pomegranate products in BCR prostate cancer patients were published in 2013 and 2014. Both of these trials used combination products in which pomegranate was $< 30\%$ of the study product and both enrolled a mixed population in which BCR patients accounted for 40% or less of the patient population. The first of these studies, by the Stenner-Liewen team at University Hospital in Zurich, was a trial of 4 weeks of 27.5% pomegranate juice blend, compared with placebo composed of the fruit juices of the blend without pomegranate juice, in patients with PSA greater than 5 ng ml$^{-1}$. For the 33 BCR patients, no significant differences were seen in PSA declines between patients on the placebo arm and those receiving the pomegranate juice blend.[5] In the second study, launched by the Thomas team at Bedford Hospital in the UK, 199 men received a food supplement tablet containing 100 mg each of pomegranate, broccoli and turmeric, and 20 mg of 5:1 green tea extract equivalent to 100 mg of green tea, or placebo, three times per day for 6 months. In the 78 participants with BCR prostate cancer, the median PSA level of men on placebo rose 80%, while the median PSA level of men on the blend rose 9% (analysis of covariance, $P < 0.001$).[6] Two aspects of this trial make it difficult for its results to contribute to our understanding of the efficacy of pomegranate in BCR prostate cancer. First, the study product was primarily composed of polyphenol-rich compounds other than pomegranate, and second, Thomas reported changes in PSA values rather than changes in PSADT used by the other trials. However, the study tablet was well tolerated and safe.

When using PSADT as the primary end point, placebo control is required because of natural increases of PSADT that are experienced by BCR patients.[32] Pantuck's group launched a larger, multicenter, double-blind, placebo-controlled study, which was published in 2015. The new study originally sought to accrue 300 patients in three arms, including pomegranate liquid extract, pomegranate juice and placebo for 12 months of treatment. Slow accrual caused the investigators to discontinue the juice arm and compare 8 oz. of liquid extract consumption with placebo. Of the 183 enrolled participants, 64 were treated with placebo, 17 with juice and 102 with pomegranate liquid extract, which contained the same compounds found in pomegranate juice with the exception of a higher proportional content of pomegranate polyphenols, primarily punicalagin and isomers, (776 mg gallic acid equivalents (GAE) /8 oz. in liquid extract[30] vs 570 mg GAE /8 oz. of juice[3]).

The primary end point of the study, difference in change in PSADT between POM-treated and control arms, was negative. In this patient population with a PSADT shorter than Pantuck's previous trial and similar to that of Paller *et al.*, the median increase in PSADT from baseline to end of treatment for each arm was greater in the placebo arm than in the liquid extract arm. In the placebo arm, median PSADT increased from 11.1 months at baseline to 15.6 months, while in the liquid extract arm, median PSADT increased from 12.9 months at baseline to 14.5 months.

A preplanned subset analysis of the 34 (22%) men with the manganese superoxide dismutase (MnSOD) AA genotype was also performed. Patients with the AA genotype experienced a greater PSADT lengthening in the liquid extract group (median PSADT increased from 13.6 to 25.6 months, $P = 0.03$), while no significant change was seen in the placebo group of MnSOD (median PSADT increased from 10.9 to 12.7 months, $P = 0.22$). No *P*-value was reported for the difference in median PSADT change between the arms in this subset analysis. MnSOD is the primary antioxidant enzyme in mitochondria. A polymorphism at codon 16 of the *MnSOD* gene in men encodes either alanine (A) or valine (V). The AA genotype has been associated with more aggressive prostate cancer and with more sensitivity to antioxidants than the VA or VV genotype. A study of the prostates of 194 deceased men showed that the AA genotype (as compared with the VA or VV genotypes together) was associated with significant prostate cancer in men older than 69 years of age (odds ratio 4.89, 95% confidence interval 1.51–15.8), but not in men younger than 70 years of age.[33] In a case–control analysis of men in the Physician's Health Study randomly assigned to beta-carotene treatment (vs placebo), men with AA genotype had a relative risk of 0.6 (95% confidence interval, 0.2–0.9; $P_{\text{interaction}} = 0.03$) for fatal prostate cancer. The association for men with the VV/VA genotype was not significant.[34] Thus, Pantuck's finding that men with the AA genotype had greater lengthening of PSADT than other men is consistent with prior studies demonstrating that antioxidants confer greater benefit in reducing prostate cancer in men with the AA genotype, a hypothesis generating finding for potential future trials of pomegranate products. Beyond the potential for further study in specific subpopulations, the clinical data provide reassurance that pomegranate products are safe for our patients, that placebo control is essential in trials enrolling BCR prostate cancer patients, and that there is no placebo-controlled evidence demonstrating that pomegranate products increase PSADT in the general BCR patient population.

### Neoadjuvant trials

Beginning in 2009, three clinical trials of pomegranate products were launched with prostate cancer patients who were planning surgery and/or radiation as definitive local therapy. The first neoadjuvant trial was a multisite study in which 70 patients were randomized to two tablets of pomegranate extract (POM Wonderful) or placebo daily for up to 4 weeks prior to radical prostatectomy. The trial was powered to detect 35% reduction in tissue 8-OHdG, an oxidative stress biomarker. A 16% reduction in 8-OHdG was seen in the pomegranate extract treatment arm vs placebo, which was not statistically significant ($P = 0.095$).

A second study sought to test two 500 mg tablets of pomegranate extract (Verdure Sciences, Noblesville, IN, USA) for 4 weeks prior to surgery at Vancouver Coastal Health in Canada, but was terminated because of low accrual.[35] A third trial in 77 prostate cancer patients prior to prostatectomy or radiation compared 3 weeks of placebo, tomato juice, and a combination of tomato, pomegranate, grape juice, green and black tea, selenium, omega-3 and soy. No significant differences were seen in PSA values between the placebo patients and either of the treatment groups.[4] In the neoadjuvant population, pomegranate products have not been shown to be effective in reducing markers of oxidative stress.

### Active surveillance trial

The Thomas study of 6 months of a food supplement tablet or placebo, described above in the Biochemically recurrent prostate cancer trials section, enrolled 121 men being managed with AS. In this AS subgroup, the mean PSA rose by 47% in the placebo arm,

while it fell slightly (0.14%) in the food supplement arm. ($P = 0.001$). The 27.7% dropout rate in the placebo group was significantly larger than the 8.2% dropout rate in the food supplement group ($P = 0.014$).[6]

### Metastatic disease trial

In the European trial of 27.5% pomegranate juice blend (Biotta) vs placebo, for 4 weeks, 61 patients (68% of total enrollment) had been diagnosed with CRPC. In the CRPC population, no significant efficacy differences were reported between the juice and placebo arms, as was true for the BCR patients in this population described above. PSA stabilization at 4 weeks was seen in 53% of CRPC patients in the juice group and 45% in the placebo group (no *P*-value reported). No CRPC patients experienced PSA decline $>50\%$ in either group.[5] In this trial, the 4-week treatment window may have been too brief to observe significant changes. Further, in patients who have progressed on anti-hormonal therapy, prostate cancer cells often use alternative pathways such as the IGF-1/AKT/mTOR pathway,[36] on which the polyphenols of pomegranate juice have no effect. Thus this population is unlikely to derive benefit from pomegranate-based therapies.

### Summary of clinical trial results

Clinical trials confirmed that pomegranate juice and extract are safe. Early promising results in BCR prostate cancer patients in phase II trials without placebo arms were not confirmed in a larger, placebo-controlled trial. An exploratory analysis showed a subset of BCR patients with the MnSOD AA genotype appeared to respond positively to the antioxidant effects of pomegranate treatment. In phase II trials of neoadjuvant patients and mCRPC patients, results using 100% pomegranate products were negative. A multicomponent food supplement with pomegranate content showed promising results in a placebo-controlled phase II study in AS and BCR prostate cancer patients.

## WHAT SHOULD PHYSICIANS TELL PROSTATE CANCER PATIENTS ABOUT POMEGRANATE JUICE?

Patients asking about pomegranate juice or extract consumption should be referred to the Prostate Cancer, Nutrition, and Dietary Supplements (PDQ)–Patient Version at the National Cancer Institute,[37] where they will find brief summaries of the source of bioactive compounds in pomegranates, and the results of preclinical studies and clinical trials in the biochemically recurrent prostate cancer patient population, concluding with the phase III trial results showing no differences in PSADTs between placebo and pomegranate arms. If future studies confirm that pomegranate products benefit patients with the MnSOD AA genotype, testing for MnSOD status may be beneficial in guiding patients. If drug–drug interaction questions arise, in the context of known problems with grapefruit juice, the patient may be told that preclinical data support the possibility of CYP3A4/CYP2C9 inhibition by pomegranate juice.[38] However, there is little clinical concern as the data in health volunteers show little effect of pomegranate juice on the pharmacokinetics of CYP-metabolized drugs, while grapefruit juice does affect the clearance of those drugs.[39]

## POTENTIAL FUTURE TRIALS

In designing future studies of pomegranate products in prostate cancer patients, we would recommend measuring biomarkers and metabolites such as MnSOD, a genetic marker of responsiveness to antioxidant treatment, 8-OHdG, a marker of oxidative stress, and urolithin A, a metabolite of pomegranate juice ellagitannins that may provide evidence of concentration of a metabolite likely to produce pharmacological effects. In selecting a target population likely to benefit, we suggest BCR patients of 70 years of age or older who have the MnSOD AA genotype. Patients with the AA MnSOD genotype experienced a near doubling of PSADT (13.6–25.6 months, $P = 0.03$) in a subset analysis of the 2015 phase III study.[7] Further, the AA genotype (as compared with the VA or VV genotypes together) was associated with significant prostate cancer in men older than 69 years of age (odds ratio 4.89, 95% confidence interval 1.51–15.8), but not in men younger than 70 years of age.[33] Given that the frequency of the MnSOD AA genotype is 25% among prostate cancer patients,[40] a placebo-controlled trial of pomegranate juice or extract targeted to these biomarker-defined patients may produce clinically valuable results. In addition, given the positive findings of Thomas *et al*.[6] in the study of the multicomponent food supplement capsule in men on AS, further study of that intervention in AS and BCR patients is warranted.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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