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A Review of Pomegranate in Prostate Cancer

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Abstract

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-OHdG, 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 multi-component food supplement tablet, including 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 biochemical recurrence.

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

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patients with mCRPC were negative. A multi-component food supplement showed promising results in a phase II study in active surveillance and BCR patients.

Keywords

Pomegranate; prostate cancer; clinical trials; dietary supplements; natural products

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, in PSA levels, and in 8-OHdG, a marker of oxidation in prostate cancer tissue. The first trial, published in 2006, showed promising increases in PSA doubling time 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 United States 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.[10] 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.[11] The National Cancer Institute web site 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).[12]

PRECLINICAL STUDIES AND MECHANISMS OF ACTION

The first preclinical study of pomegranate products in prostate cancer, by Gil, *et al.* in 2000, measured Trolox equivalent antioxidant capacity (TEAC) 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,[13] both of which had shown promising antiproliferative activity in preclinical prostate cancer models.[14, 15] Gil also reported that pomegranate juice contains anthocyanins, ellagic acid derivatives, and hydrolyzable tannins such as punicalagins with 90% of the antioxidant activity provided by the punicalagins and other hydrolysable tannins.[13] That same year Aviram's 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 antiatherogenic effect of pomegranate on lipoprotein, macrophage, and platelets.[16, 17] In 2002, Kim *et al.* studied the potential antiproliferative effects of polyphenols derived from fresh 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.[18] Two earlier studies had reported that pomegranate juice contains anthocyanins, other flavonoids and phenolic acids,[19] and pomegranate pericarp contains tannins and ellagitannins.[20] Commercial juice is produced by pressing whole fruits, so the polyphenols of the fruit juice are enriched by ellagitannins[18] of the pericarp. Researchers had already found that cancer cell growth was inhibited, both in vitro and in vivo, by flavonoids[21] and tannins.[22]

Based on the growing body of preclinical evidence about the anti-proliferative activity of the active components of pomegranate juice, a phase II clinical trial of pomegranate juice in prostate cancer patients experiencing biochemical recurrence following definitive local therapy was launched in 2003. Results of that first trial were published in 2006[3] and are described, along with results from six others 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.* 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.[23]

Additional preclinical justification for human trials of pomegranate in prostate cancer was provided in 2005 when Malik *et al.* found that an extract made from pomegranate juice, containing anthocyanins and ellagitannins, had anti-proliferative and pro-apoptotic effects that are produced through modulation of cyclin-dependent kinase (cdk) in PC3 cells.[24] 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 (PARP) and Bcl-2-associated X protein (Bax), in PC3 cells, and downregulated proteins that block apoptosis, such as B-cell lymphoma 2 (Bcl-2).[25]

Two years later Pantuck *et al.* demonstrated that powdered pomegranate extract (POM Wonderful, Los Angeles, CA), made from fruit residue after pressing for juice, has an inhibitory effect on the nuclear factor-kappaB (NF-κB) 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 NF-κB activity that takes place during the transition from androgen-dependence to androgen-independence in LAPC4 xenograft tumors.[26] NF-κB has been shown to be an important predictor of biochemical recurrence following local therapy in prostate cancer patients.[27, 28] More recently Wang *et al.* provided evidence that pomegranate extract may be effective in treating metastatic castration-resistant prostate cancer. 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.[29]

Results from these preclinical studies showing extensive antioxidant and anti-proliferative activity of pomegranate products resulted in the launch of ten 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 through July 10, 2016. Three trials were excluded for different reasons. A trial of powdered pomegranate extract (Venture Sciences, Noblesville, IN) in neoadjuvant patients (NCT01100866), was closed due to slow accrual, and another trial of powdered pomegranate extract (POM Wonderful) in patients undergoing active surveillance (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[30] 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 AG, Tägerwilen, Switzerland), a powdered extract combining equal amounts of active compounds from pomegranate, green tea, broccoli and turmeric, (Helsinn Healthcare S.A., Lugano, Switzerland), and a combination of pomegranate and grape juice (Tine SA, 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 prostate-specific antigen (PSA) level is known as biochemical recurrence (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 active surveillance 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 2 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 and Carducci 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 gram (47) or 3 grams (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 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 study reported much larger PSADT differences than the 2013 Paller study. Such differences could be explained by differences in the patient population as Pantuck limited eligibility to patients with PSA <5 ng/mL, while 32% of patients in the Paller trial had baseline PSA levels >5 ng/mL, ranging up to 32 ng/mL, 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 2013 and Pantuck 2006 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 less than 30% of the study product and both enrolled a mixed population in which BCR patients accounted 40% or less of the patient population. The first of these studies, by Stenner-Liewen team at University Hospital in Zurich, was a trial of four 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 five ng/ml. For the 33 BCR patients, no significant differences were seen in PSA declines between patients on the placebo arm and those receiving 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 5:1green tea extract equivalent to 100 mg of green tea, or placebo, three times per day for six 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% (ANCOVA, 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 PSA doubling times used by the other trials. However, the study tablet was well tolerated and safe.

When using PSADT as the primary endpoint, placebo control is required because of natural increases of PSADT that are experienced by BCR patients.[32] Pantuck's group launched a larger, multi-center, doubled-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[33] vs. 570 mg GAE/8 oz. of juice[3]).

The primary endpoint 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 months 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 (OR 4.89, 95% CI 1.51–15.8), but not in men younger than 70 years.[34] In a case control analysis of men in the Physician's Health Study randomly assigned to beta-carotene treatment (versus placebo), men with AA genotype had a RR of 0.6 (95% CI, 0.2–0.9; $P_{interaction}$ = 0.03) for fatal prostate cancer. The association for men with the VV/VA genotype was not significant.[35] 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 provides 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 PSA doubling time 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 four weeks prior to radical prostatectomy. The trial was powered to detect 35% reduction in tissue 8-hydroxy-2-deoxyguanosine (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) for four weeks prior to surgery at Vancouver Coastal Health in Canada, but was terminated because of low accrual.[36] A third trial in 77 prostate cancer patients prior to prostatectomy or radiation, compared three 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 six months of a food supplement tablet or placebo, described above in the Biochemically recurrent prostate cancer trials section, enrolled 121 men being managed with active surveillance (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 four weeks, 61 patients (68% of total enrollment) had been diagnosed with castration resistant prostate cancer (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 four 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 four-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,[37] 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 multi-component food supplement with pomegranate content showed promising results in a placebo-controlled phase II study in active surveillance 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,[38] where they will find brief summaries of the source of bioactive compounds in pomegranates, and the results of preclinical studies and clinical trials in biochemically recurrent prostate cancer patient population, concluding with the phase III trial results showing no differences in PSA doubling times 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.[39] However, there is little clinical concern as the data in health volunteers shows little effect of pomegranate juice on the pharmacokinetics of CYP metabolized drugs, while grapefruit juice does affect the clearance of those drugs.[40]

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 pharmacologic effects. In selecting a target population likely to benefit, we suggest BCR patients 70 years old or older who have the MnSOD AA genotype. Patients with the AA MnSOD genotype experienced a near doubling of PSADT (13.6 to 25.6 months, p=0.03) in a subset analysis of the 2015 phase 3 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 (OR 4.89, 95% CI 1.51–15.8), but not in men younger than 70 years.[34] Given that the frequency of the MnSOD AA genotype is 25% among prostate cancer patients,[41] 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, in the study of the multicomponent food supplement capsule in men on AS,[6] further study of that intervention in AS and BCR patients is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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/day (570 mg/day GAE)	33 months	Open, uncontrolled	Mean PSADT increased from 15.6 months to 54.7 months (p=001). No serious AEs.
Stenner-Liewen *et al*.[5] (European trial, no NCT #) Sponsor: Biotta AG	CRPC 65%, BCR 35%	97	Juice blend of 27.5% pomegranate, plus pear purée, white tea, agave concentrate, aronia berry juice	500 mL/day (1147 mg/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 at al[7] NCT00336934 Sponsor: POM Wonderful	BCR	183	Liquid pomegranate extract and standard juice	8 oz/day (776 mg/day GAE[33])	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/day of pom. 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, 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/day (755–2265 mg/day GAE[33])	13.8 months	Low dose (45) vs high dose (47)	Significant lengthening of median PSADT in treatment group 11.9 to 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 at 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/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.

Study/NCT	Target population	N	Intervention	Dose	Mean Duration	Design (n)	Results
Freedland *et al.*[1] NCT00719030 Sponsor: POM Wonderful	Neoadjuvant (prior to prostatectomy)	69	Powdered pomegranate extract	1000 mg/day (600 mg/day GAE)	4 weeks	Extract (36) vs. placebo (33)	Significant increase in urolithin A detection (34% to 64%, p=0.031) and non-significant 16% reduction (p=0.095) in 8-OHdG in treatment arm. No serious AEs.

AS: Active surveillance: observation only, no local treatment planned; BCR: Biochemically recurrent prostate cancer, e.g. men experiencing rising PSA following definitive local therapy
CRPC: Castration resistant prostate cancer
AE: adverse eventsGAE: gallic acid equivalents (polyphenols)
8-OHdG: 8-hydroxy-2-deoxyguanosine
MnSOD AA: manganese superoxide dismutase AA genotype
RCN: The Research Council of Norway
NCS: The Norwegian Cancer Society