# ProDiet: A Phase II Randomized Placebo-Controlled Trial of Green Tea Catechins and Lycopene in Men at Increased Risk of Prostate Cancer

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The authors declare no potential conflicts of interest.

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**Abbreviations**: ARI: 5-alpha-reductase inhibitor; EGCG: flavan-3-ol ()-epigallocatechin-3-gallate; HGPIN: high grade prostatic intraepithelial neoplasia; ProtecT: prostate cancer screening and treatment trial; ProDiet: Prostate and Diet study; ProMPT: prostate mechanisms of progression and treatment; PSA: Prostate Specific Antigen; RCT: randomised controlled trial

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## Disclosure of Potential Conflicts of Interest

The manufacturers provided capsules at no cost (lycopene – LycoRed Ltd, Beer Sheva, Israel and green tea – Frutarom Ltd, Reinach, Switzerland) although they had no further role in the design, collection, analysis or interpretation of data or the decision to submit the article for publication. No potential conflicts of interest were disclosed by the authors.

## ABSTRACT

Epidemiological studies suggest that diet can alter prostate cancer risk. This study aimed to establish the feasibility and acceptability of dietary modification in men at increased risk of prostate cancer. Men were invited with a prostate specific antigen (PSA) level of 2.0-2.95 ng/mL or 3.0-19.95 ng/mL with negative prostate biopsies. Randomization (3x3 factorial design) to daily green tea and lycopene: green tea drink (3 cups, unblinded) or capsules (blinded, 600 mg flavan-3-ol ()-epigallocatechin-3-gallate (EGCG) or placebo) and lycopene-rich foods (unblinded) or capsules (blinded, 15 mg lycopene or placebo) for six months. Primary endpoints were randomization rates and intervention adherence (blinded assessment of metabolites) at six months with secondary endpoints of acceptability (from interviews), safety, weight, blood pressure and PSA. A total of 133/469 (28.4%) men approached agreed to be randomized and 132 were followed-up (99.2%). Mean lycopene was 1.28 (95% confidence intervals (CI) 1.09, 1.50, p = 0.003) times higher in the lycopene capsule group and 1.42 (95% CI 1.21-1.66, p<0.001) times higher in the lycopene-enriched diet group compared to placebo capsules. Median EGCG was 10.7 nM (95% CI 7.0, 32.0) higher in in the active capsule group and 20.0 nM (95% CI 0.0, 19.0) higher in the green tea drink group compared with placebo capsules (both p<0.001). All interventions were acceptable and well tolerated although men preferred the capsules. Dietary prevention is acceptable to men at risk of prostate cancer. This intervention trial demonstrates that a chemoprevention clinical trial is feasible.

## Introduction

Prostate cancer is the commonest non-cutaneous male malignancy worldwide with higher incidence in developed countries, in part due to screening with prostate specific antigen (PSA)(1). Around three quarters of men with an elevated PSA will not have cancer diagnosed immediately so safe and effective chemoprevention would be beneficial as they are at risk of future diagnosis (2). Randomized controlled trials (RCT) of prostate cancer prevention have included pharmaceutical and nutritional agents but with limited success. Finasteride (a 5-alpha-reductase inhibitor (ARI)) reduced prostate cancer risk in an RCT but the increase of high grade tumors in the finasteride group and other adverse effects prevented licensing (3). Dutasteride (another ARI) also showed a lower incidence of prostate cancer but with a small excess of cardiac failure events (14 extra cases in 4,105 men, p = 0.03) (4) More recently, the risk of higher grade cancers on 5-ARIs was not confirmed although there is an increased sexual side effect profile (5). The lower prostate cancer incidence in a lung cancer prevention trial for smokers with vitamin E (6) and in a selenium trial for melanoma patients (7) informed the design of the selenium and vitamin E phase III SELECT trial. However, despite being a well-conducted RCT with an intensive recruitment strategy and high enrolment of ethnic minority participants there were no benefits at a five-year interim analysis of SELECT. The trial was stopped prematurely and subsequently a higher prostate cancer incidence was shown in the vitamin E group (8).

Promising dietary chemoprevention agents based on pre-clinical and observational studies include lycopene, the major carotenoid in tomatoes. Lycopene is an active singlet oxygen quencher which assists DNA repair mechanisms (9). The WCRF/AICR systematic review categorized lycopene as “probable for decreased prostate cancer risk” (10) which was revised to “limited - no conclusion” in 2014 (11) One of the few RCTs of lycopene supplementation for prostate cancer prevention in Afro-Caribbean men with high grade prostatic intraepithelial neoplasia (HGPIN, a potential prostate cancer precursor) did not alter PSA levels (12). However, participants were not blinded, follow-up was only four months and the acceptability of lycopene was not assessed in this trial.

Prostate cancer incidence in Asian countries with high consumption of green tea such as Japan is lower than in western countries (13). Epigallocatechin-3-gallate

(EGCG) is the most abundant and potent catechin in green tea with anti-tumor activities on inflammatory, insulin growth factor and androgen signalling pathways (14). The WCRF/AICR review found “limited- no conclusions” possible for green tea for prostate cancer although a more recent review found it preventative (15). A recent small trial of EGCG capsules in men with HGPIN concluded that there was no difference in prostate cancer rates on re-biopsy at one year, although PSA levels were reduced by around 1 ng/ml and the capsules were well tolerated (16).

Evidence is now required from RCTs of dietary interventions for prostate cancer prevention to detect clinical benefits and harms. However, given the paucity of randomized trials we firstly aimed to investigate the acceptability and feasibility of dietary modification and supplementation for green tea and lycopene in men at increased risk of prostate cancer in a placebo-controlled trial. Here we report the ProDiet (Prostate Diet) feasibility trial primary and secondary endpoints.

## Materials and Methods

### Study design

This was a placebo-controlled phase II randomized trial which compared green tea and lycopene dietary modification and capsules in men with PSA results between 2.0 and 2.974 ng/mL, or between 2.975-19.95 ng/mL with a negative biopsy. The study was approved by the UK Healthcare Research Authority Trent Multicentre Research Ethics Committee (08/H0405/61), conducted according to Declaration of Helsinki, 1964 and the trial number is ISCTRN 95931417.

### Recruitment and eligibility

Men who had participated in the Prostate testing for cancer and Treatment (ProtecT) trial at nine family practices in a UK city were invited to the ProDiet study between 2009-2010. The ProtecT trial (ISCTRN 20141297) is a population-based randomized controlled trial of treatments for localized prostate cancer (17) In brief, 82,849 men aged 50-69 years were invited for PSA testing in nine centers and those with a raised PSA result were invited for standardized prostate biopsies. No ProtecT tests were offered if the PSA result was below 3.0 ng/mL or for negative biopsy results.

Men attended a ProDiet appointment at their family practice with a study nurse who assessed eligibility, explained the potential risks and benefits of participation and obtained written consent. Men were excluded with a history of allergies to lycopene-containing foods or green tea; current or prior prostate cancer; major co-morbidities or 5-ARI medication.

### Randomization and blinding

Participants were randomly allocated to one of three lycopene interventions *and* to one of three green tea interventions using a blocked random allocation (1:1:1 ratio)(generated by the trial statistician [CM] using the Stata uniform() function) so that around 14 men were allocated to each of the nine lycopene and green tea intervention combinations. The intention had been to stratify the allocation by baseline PSA; however, this was impractical with opaque envelopes for allocation.

The allocation was concealed from the study nurse recruiting individuals until the participant's details were logged electronically with the research centre, the nurse then opening the next numbered envelope containing the participant's allocation. If the participant was allocated to capsules, the bottle number would be indicated.

Participants allocated to green tea drink were given a month's supply, and those to lycopene diet were given verbal and written advice (each intervention had a patient information leaflet).

To maintain blinding of participants and the study nurse, active and placebo capsules were very similar in appearance and provided to the study nurse in sealed packs. There was no blinding of participants allocated to dietary modification.

**Interventions**

Men in the lycopene dietary group were advised to consume one to two portions of preferably cooked tomatoes daily (examples given included a bowl of soup, a heaped tablespoon of tomato puree or ketchup, two tinned tomatoes, one medium fresh tomato or a glass of tomato juice). Fruits such as watermelon or pink grapefruit were allowed, but men were advised that their lycopene content was lower than tomatoes. No foods were provided to this group. The other lycopene interventions comprised one daily gel capsule of 15 mg tomato-derived extract of lycopene (*Solanum lycopersicon* L. Solanaceae, Lyc-O-Mato®, Lycored Ltd, Beer Sheva, Israel, authorized as dietary supplement in the UK) or a matched placebo capsule (Lycored Ltd) taken with a meal with water. The green tea (GT) interventions consisted of either drinking at least three cups (two UK mugs) of green tea daily (*Camellia sinensis* L, Theaceae, around 600 ml/day, green tea bags e.g. PG Tips, Unilever Ltd, provided by the study), or two 300 mg green tea leaf-derived extract capsules (600 mg/d EGCG, Frutarom Ltd, Reinach, Switzerland, authorised as a dietary supplement in the UK) or two matched placebo capsules (Frutarom Ltd). The dose was planned as 800 mg/d but was replaced by 600 mg/d as the supplier only manufactured 300 mg capsules.

Participants were provided with the first month's supply of capsules and/or green tea bags after randomization, then by post at one and three months (providing a six month supply). The research nurse telephoned men at one month to arrange supplies and give further advice regarding the interventions. Participants were given weekly study logs to aid compliance and to return unused supplies at six months. No foods or supplements were prohibited during follow-up. It was planned to advise all groups to consume five fruits or vegetables daily but this was removed as it may have hindered adherence and acceptability. The design and delivery of participant information was informed by the Theory of Planned Behaviour (18) and men received a study fridge magnet (19) and there was a study website and newsletter.

**Participant follow up**

The study nurse recorded socio-demographic information, weight, blood pressure and clinical characteristics at recruitment and took non-fasting blood samples for PSA and metabolite analyses. Participants completed a paper questionnaire following randomization (baseline), at one (postal) and at six months, including a food frequency questionnaire (FFQ), smoking status and consumption of alcohol, the Hospital Anxiety and Depression Scale (20), Profile of Moods States (21) and International Continence Society Male Short Form (22). Additional questions on intervention compliance and satisfaction, adverse events in the preceding month and dietary changes were completed during follow-up. Participants were given an adverse event form with a freepost envelope. The nurse telephoned participants at one month to discuss PSA results, interventions and to arrange further supplies (planned as in-person so PSA and weight were not measured at one month). At the six-month appointment the nurse recorded weight and blood pressure, asked about intervention adherence and acceptability and took blood samples. Serum samples were separated by centrifugation and were stored at -80$^0$C until analysis. Body mass index (BMI) used height measured in the ProMPT translational study linked to the ProtecT trial (60% uptake). Follow-up was completed between 2009 to 2010.

**Laboratory assessments**

Lycopene, green tea metabolites and PSA were measured by laboratory staff blinded to the allocation (samples were identified by study number). PSA was measured at the local hospital which used the UK National Health Service External Quality Assessment for PSA. Plasma lycopene was measured by reversed-phase high-performance liquid chromatography (HPLC) with diode array detection following extraction into heptane (23) Plasma catechins, including ()-epicatechin-*O-glucuronide*, () epicatechin-sulfate, EGCG and 5-(dihyroxyphenyl)-Ɣ-valerolactone above 1.0 nmol/L were measured using HPLC-mass spectrometry (24), (25).

**Dietary assessment and analysis**

Dietary intake was assessed using a validated 117-item food frequency questionnaire (FFQ) adapted from the UK EPIC study (26) with frequency reported across nine categories from “never/less than once per month” to “six or more times per

day" for the previous six months (green tea was added in the same format). Analyses were conducted as described previously (27) and men were excluded from dietary analyses if they were assessed as misreporting energy intake [<800kcal/d or >4000kcal/d (28). Alcohol consumption was categorised as above or below national recommendations (20 units/week).

**Qualitative interviews and analysis (assessment of acceptability and attitudes)**

Men were interviewed at around 6 and 30 weeks after randomization to assess intervention acceptability and men's experience of the interventions (21 men as one participant declined after the baseline interview because he felt he had nothing further to contribute). Interviews were fully transcribed with baseline results published previously (27), (18).

**Statistical analysis and sample size calculation**

Primary outcomes were recruitment (randomization rate) and adherence to interventions (metabolite levels). It was, therefore, planned to invite around 250 men until 126 men were recruited, allowing an anticipated 50% recruitment rate to be estimated with 95% confidence interval from 44% to 56%. If 126 men were enrolled, the study would have 90% power at the 5% significance level to detect a true 67% increase in circulating lycopene and green tea metabolites between the placebo and intervention groups (including accommodation for skewed distribution of measures) at six months (29). There were no planned interim analyses or stopping guidelines.

Analyses were conducted on an intention-to-treat basis using Stata 14 (StataCorp, College Station, TX, USA). Analysis of covariance (ANCOVA) compared the log-transformed lycopene levels across lycopene groups at six months adjusted for transformed baseline lycopene levels. The exponentiated coefficients are the ratio of the geometric mean lycopene levels for active lycopene groups versus placebo capsules. Many green tea values were zero so the non-parametric generalized Hodges-Lehmannn (30) median difference (plasma values) and two-proportion z test (dietary reports) were used to compare active and placebo distributions and calculate 95% Cis (p-value calculated using the Mann-Whitney test).

As this was a factorial design, we assessed if there was an interaction between lycopene and green tea interventions on six-month lycopene levels. To maximise statistical power an 'active' group (dietary advice and lycopene capsule groups) was

compared with the placebo group. Baseline lycopene was included as a covariate, and a dummy variable identifying participants receiving both active lycopene and green tea interventions allowed the evidence for an interaction to be evaluated. There was no evidence of an interaction between lycopene and green tea on serum lycopene levels (p for interaction=0.4), allowing the two interventions to be examined separately.

ANCOVA was used to compare mean PSA levels, systolic blood pressure and weight between intervention groups and placebo for green tea and lycopene at six months (corresponding baseline measure of the outcome included as a covariate). The distribution of PSA results was highly skewed, so was log-transformed before analysis.

## Results

### Baseline characteristics and randomization

Of 469 men approached between December 2009 and May 2010, 133 were randomized (28.4%, 95% CI 24.3%-32.7%) giving around 45 participants in each lycopene and green tea intervention (consort diagram shown in Figure 1). Of these, 132 men attended six-month follow-up and 131 (98.5%) gave blood. Table 1 displays the baseline characteristics which were well matched by allocated intervention. In addition, 132 men were of white ethnicity and around half had a managerial occupation.

### Primary endpoint-adherence

Plasma levels at six months were higher in the lycopene capsule and dietary advice groups than in the placebo group, although the pre-specified target difference of 67% was not met (Table 2). Plasma metabolites (EGCG) were higher in the green tea drink and capsule groups than the pre-specified target difference and were undetectable in the placebo group (Table 2).

### Secondary endpoints

*Adherence and dietary intake.* Consumption of lycopene-containing foods was highest in the dietary advice group with no increase reported in capsule groups (Table 2 and Supplementary Figure 1). The proportion of men who reported that they drank green tea daily increased to 79% in the tea drinking group at six months but was low and unaltered in both capsule groups (Table 2 and Supplementary Figure 1).

*Acceptability of interventions.* Men stated in interviews that they were confident about adhering to their allocated options by quickly and easily establishing a routine to prompt them regarding their interventions (Table 3). Routines were assisted by taking capsules at meals or with prescribed medicines, whilst green tea drinkers either swapped some or all the normal black tea or added green tea drinks e.g. at meals. Men randomized to dietary lycopene often added tomatoes to recipes, lunch plates or sandwiches and tomato juice was very popular. Men used the ProDiet log but typically discontinued it once a routine became established, often in the early days/weeks. Changes to their established routine (e.g. holidays or eating out) were the most commonly reported barriers to adherence because men forgot or chose not to take interventions with them (Table 3). However, many men reported always being able to adhere to the

interventions. Some men were surprised that they found green tea palatable and few reported significantly disliking it. Men randomized to the lycopene-rich diet often reported liking tomatoes and so not minding or finding it enjoyable to increase their intake. Most men regarded capsules as 'supplements' rather than medication, which may have assisted those men who usually disliked taking medication.

In future, men reported they would prefer capsules to dietary options for green tea (102/132, 77.3% preferred capsules; 26/132, 19.7% preferred drink) and lycopene (88/132, 66.7% preferred capsules, 41/132, 31.1% preferred dietary changes). Around half of the participants intended to continue with a tomato-rich diet (64/132 48.5%) after the trial and around one third drinking green tea (45/132, 34.1%).

*Adverse events.* The frequency was generally low except for nocturia (night time urinary frequency), insomnia and hypertension which occurred in similar frequencies across all groups (Table 4).

*Clinical outcomes.* PSA levels did not differ between lycopene or green tea groups at six months (Table 5). Systolic blood pressure and weight were also comparable between all green tea and lycopene groups (Table 5).

## Discussion

We report a randomized feasibility trial of green tea and lycopene supplementation in men at increased risk of prostate cancer. Nearly one third of men agreed to be randomized to lycopene and green tea capsules or dietary options for six months. Lycopene and green tea (EGCG) plasma concentrations were higher in participants randomized to active capsule or dietary options compared to those randomized to placebo capsules. Men's accounts from interviews revealed that they quickly established routines to enhance adherence by incorporating interventions into daily life. There were also no major differences in adverse events between groups. PSA, systolic blood pressure and weight were comparable between groups, although the trial was not designed to identify differences in these endpoints.

To our knowledge, this is the first placebo-controlled randomized trial of lycopene and green tea to include dietary options in men at increased risk of prostate cancer. The factorial design maximised the options tested and the standardized ProtecT trial prostate cancer detection process ensured a well-characterised ProDiet population. Several features helped increase trial quality such as measures to conceal random allocation, blinding of participants to capsule options and outcome assessors. Self-reported consumption of green tea and lycopene-rich foods remained stable in men randomized to placebo capsules so contamination was low which implies that participant blinding had been successful. Adherence and acceptability were assessed in multiple ways, including interviews which evaluated men's attitudes towards interventions. The trial design was pragmatic with no run-in period to remove non-compliant individuals, dietary restrictions or provision of multi-vitamins (8).

Recruitment to cancer chemoprevention phase II trials is difficult (2) and was lower than planned in this trial, whereas an intensive process was required in the SELECT trial to ensure success (8). Adherence was high in ProDiet at six months but might have been lower beforehand as there were no interim assessments, although interviews indicated that men established routines to enhance adherence. Metabolites were not measured from fasted participants as this would have restricted participants attending afternoon appointments. Non-fasted measurements may have lowered values reported here although they were comparable with lycopene results from several studies (31) (32). The dose of green tea could have also been increased above 600mg/L but was comparable to other prostate cancer prevention studies (15) and the equivalent of at least six green tea cups daily (as consumed in Japan) was unlikely to

acceptable in the UK. There are some other limitations as the trial recruited previous trial participants whom might have been more disposed to adhere to dietary interventions than the general population. Participants were also predominantly white (as in the ProtecT trial), thus reducing generalisation to other ethnicities with different prostate cancer risks. UK Afro-Caribbean men revealed in interviews that they were quite heavily involved in food preparation with tomatoes being central to their diet in contrast to most ProDiet and ProtecT participants (27), (18), (33).

Lycopene intake and circulating lycopene were associated with a reduced risk of prostate cancer (34), (35) in some meta-analyses, although not universally (11). A recent meta-analysis suggested that there was a 3% reduction in prostate cancer incidence per mg/day increase in dietary lycopene intake (95% CI 0.94-0.99) (35) which matches the increase seen in lycopene dietary consumption reported in this trial. The ProDiet dietary lycopene intervention equates to tomato consumption previously associated with a reduced prostate cancer risk in ProtecT trial participants (36). However, a small placebo-controlled trial of lycopene supplementation in men with HGPIN showed no differences in expression of tissue markers for proliferation or cell cycle inhibition (MCM-2 and p27, primary endpoints), PSA or cancer rates on re-biopsy at six months (37). Lycopene has cardiovascular benefits although not through lowering blood pressure so different endpoints would be needed in a definitive trial to measure its broader impacts (38).

Recent systematic reviews suggest a possible role for green tea in prostate cancer prevention for HGPIN (39), (14), (40) but evidence is conflicting for overall prostate cancer incidence (41). Polyphenols were detected in prostate tissue of men with prostate cancer who had consumed green tea (but not black tea or water) prior to radical prostatectomy (42) and showed systemic anti-oxidant effects. The second trial of green tea capsules for 3-6 weeks before prostatectomy showed no changes in PSA nor prostate tissue biomarkers of cell proliferation, apoptosis or angiogenesis which the authors hypothesised may have been due to rapid clearance or poor bioaccumulation (43).

The mode of action of most chemoprevention agents remains largely unknown and the concept for prostate cancer has been deemed a failure following the SELECT and finasteride trials (44). However, preclinical evidence should be used to identify biologically active agents to enhance their likelihood of success in clinical trials (2), (45). In one example, aspirin has recently been recommended for colorectal cancer

prevention in the USA (46). The UK Add-Aspirin secondary chemoprevention trial with five years of aspirin or placebo in men with high risk localised prostate cancer has an survival endpoint including prostate cancer and a prostate-specific endpoint of biochemical-failure-free survival in around 2,000 patients (47). A phase III trial of lycopene, green tea or other chemoprevention agents would need to be of a similar size to the prostate cohort of the Add-Aspirin trial with a biological target, incidence endpoints and a good safety profile (45).

In conclusion, men at increased risk of prostate cancer adhered successfully to lycopene and green tea dietary and capsule interventions for six months with few side effects. Therefore, although recruitment was moderate, dietary interventions can be evaluated in clinical effectiveness randomized trials.

**Authors' Contributions**

**Conception and design:** JA Lane, C Metcalfe

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## References

1. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, et al. International variation in prostate cancer incidence and mortality rates. European urology. 2012;61(6):1079-92.
2. Bosland MC. Is There a Future for Chemoprevention of Prostate Cancer? Cancer Prev Res (Phila). 2016;9(8):642-7.
3. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. New England Journal of Medicine. 2003;349(3):215-24.
4. Andriole GL, Bostwick DG, Brawley OW, Gomella LG, Marberger M, Montorsi F, et al. Effect of Dutasteride on the Risk of Prostate Cancer. New England Journal of Medicine. 2010;362(13):1192-202.
5. Vermana G, Hamilton R, J., Andriole GL, Freedland S, J. Chemoprevention of Prostate Cancer. Annual review of medicine. 2014;65:111-23.
6. Alpha-Tocopherol BCCPSG. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med. 1994;330(15):1029-35.
7. Clark LC. Effects of selenium supplementation for cancer prevention. Jama. 1996;276(24):1957-63.
8. Klein EA. Vitamin E and the risk of prostate cancer. Jama. 2011;306(14):1549-56.
9. Chen J, Song Y, Zhang L. Effect of Lycopene Supplementation on Oxidative Stress: An exploratory Systematic Review and Meta-Analysis of Randomised Controlled Trials. 16. 2013;5:361-74.
10. World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington DC: AICR; 2007.
11. Research WCRFIAIfC. World Cancer Research Fund International/American Institute for Cancer Research Continuous Update Project Report: Diet, Nutrition, Physical Activity, and Prostate Cancer. 2014. . 2014.
12. Bunker CH, McDonald AC, Evans RW, de la Rosa N, Boumosleh JM, Patrick AL. A randomized trial of lycopene supplementation in Tobago men with high prostate cancer risk. Nutrition and cancer. 2007;57(2):130-7.
13. Mandair D, Rossi RE, Pericleous M, Whyand T, Caplin ME. Prostate cancer and the influence of dietary factors and supplements: a systematic review. Nutrition & Metabolism. 2014;11(1):30.
14. Johnson JJ, Bailey HH, Mukhtar H. Green tea polyphenols for prostate cancer chemoprevention: a translational perspective. Phytomedicine. 2010;17(1):3-13.
15. Jacob SA, Khan TM, Lee LH. The Effect of Green Tea Consumption on Prostate Cancer Risk and Progression: A Systematic Review. Nutrition and cancer. 2017;69(3):353-64.
16. Kumar NB, Pow-Sang J, Egan KM, Spiess PE, Dickinson S, Salup R, et al. Randomized, placebo-controlled trial of green tea catechins for prostate cancer prevention. Cancer Prev Res (Phila). 2015;8(10):879-87.
17. Lane JA, Donovan JL, Davis M, Walsh E, Dedman D, Down L, et al. Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial. The Lancet Oncology. 2014;15(10):1109-18.

18. Horwood JP, Avery KNL, Metcalfe C, Donovan JL, Hamdy FC, Neal DE, et al. Men's knowledge and attitudes towards dietary prevention of a prostate cancer diagnosis: a qualitative study. Bmc Cancer. 2014;14.
19. Brueton VC, Tierney JF, Stenning S, Meredith S, Harding S, Nazareth I, et al. Strategies to improve retention in randomised trials: a Cochrane systematic review and meta-analysis. BMJ Open. 2014;4(2).
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
21. Horowitz M, Adler N, Kegeles S. A scale for measuring the occurrence of positive states of mind: a preliminary report. Psychosom Med. 1988;50(5):477-83.
22. Donovan JL, Peters TJ, Abrams P, Brookes ST, De la Rosette JJMCH, Schafer W. Scoring the short form ICSmaleSF questionnaire. Journal of Urology. 2000;164(6):1948-55.
23. Craft NE, Wise SA, Soares JH. Optimisation of an isocratic high performance liquid chromatograhy separation of carotenoids. Journal of Chromatography. 1992;589(1-2):171-6.
24. Stalmach A, Troufflard S, Serafini M, Crozier A. Absorption, metabolism and excretion of Choladi green tea flavan-3-ols by humans. Molecular Nutrition & Food Research. 2009;53:S44-S53.
25. Ottaviani JL. Intake of dietary procyanidinis does not contribute to the pool of circulationg flavanols in humans. American Journal of Clinical Nutrition. 2012;95(4):851-8.
26. Bingham S, Welch A, McTaggart A, Mulligan A, Runswick S, Luben R, et al. Nutritional methods in the European Prospective Investigation of Cancer in Norfolk. Public Health Nutr. 2001;4(3):847-58.
27. Avery KNL, Donovan JL, Horwood J, Neal DE, Hamdy FC, Parker C, et al. The importance of dietary change for men diagnosed with and at risk of prostate cancer: a multi-centre interview study with men, their partners and health professionals. Bmc Family Practice. 2014;15.
28. Willett W. Nutritional Epidemiology. Third ed. New York, USA: Oxford University Press; 2012.
29. Wolfe R, Carlin JB. Sample-size calculation for a log-transformed outcome measure. Control Clinical Trials. 1999;20(6):547-54.
30. Hodges JL, Lehmann EL. Estimates of location based on rank tests. The Annals of Mathematical Statistics. 1963;34:598-611.
31. Devaraj S, Mathur S, Basu A, Aung HH, Vasu VT, Meyers S, et al. A dose-response study on the effects of purified lycopene supplementation on biomarkers of oxidative stress. Journal of the American College of Nutrition. 2008;27(2):267-73.
32. Mayne ST, Cartmel B, Silva F, Kim CS, Fallon BG, Briskin K, et al. Plasma lycopene concentrations in humans are determined by lycopene intake, plasma cholesterol concentrations and selected demographic factors. Journal of Nutrition. 1999;129(4):849-54.
33. Er V, Lane JA, Martin RM, Persad R, Chinegwundoh F, Njoku V, et al. Barriers and facilitators to healthy lifestyle and acceptability of a dietary and physical activity intervention among African Caribbean prostate cancer survivors in the UK: a qualitative study. BMJ Open. 2017.
34. Xu X, Li J, Wang X, Wang S, Meng S, Zhu Y, et al. Tomato consumption and prostate cancer risk: a systematic review and meta-analysis. Scientific Reports. 2016;6:37091.

35. Wang Y, Cui R, Xiao Y, Fang J, Xu Q. Effect of Carotene and Lycopene on the Risk of Prostate Cancer: A Systematic Review and Dose-Response Meta-Analysis of Observational Studies. PloS one. 2015;10(9):e0137427.
36. Er V, Lane JA, Martin RM, Emmett P, Gilbert R, Avery KNL, et al. Adherence to dietary and lifestyle recommendations and prostate cancer risk in the Prostate Testing for Cancer and Treatment (ProtecT) trial. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2014;23(10):2066-77.
37. Gann PH, Deaton RJ, Rueter EE, van Breemen RB, Nonn L, Macias V, et al. A Phase II Randomized Trial of Lycopene-Rich Tomato Extract Among Men with High-Grade Prostatic Intraepithelial Neoplasia. Nutrition and cancer. 2015;67(7):1104-12.
38. Cheng HM, Koutsidis G, Lodge JK, Ashor A, Siervo M, Lara J. Tomato and lycopene supplementation and cardiovascular risk factors: A systematic review and meta-analysis. Atherosclerosis. 2017;257:100-8.
39. Cui K. Chemoprevention of prostate cancer in men with high-grade prostatic intraepithelial neoplasia (HGPIN): a systematic review and adjusted indirect treatment comparison. Oncotarget. 2017;8(22):36674-84.
40. Guo Y, Zhi F, Chen P, Zhao K, Xiang H, Mao Q, et al. Green tea and the risk of prostate cancer: A systematic review and meta-analysis. Medicine. 2017;96(13):e6426.
41. Lin Y-w, Hu Z-h, Wang X, Mao Q-q, Qin J, Zheng X-y, et al. Tea consumption and prostate cancer: an updated meta-analysis. World Journal of Surgical Oncology. 2014;12:38-.
42. Henning SM, Wang P, Said JW, Huang M, Grogan T, Elashoff D, et al. Randomized clinical trial of brewed green and black tea in men with prostate cancer prior to prostatectomy. The Prostate. 2015;75(5):550-9.
43. Nguyen MM, Ahmann FR, Nagle RB, Hsu C-H, Tangrea JA, Parnes HL, et al. Randomized, Double-blind, Placebo Controlled Trial of Polyphenon E in Prostate Cancer Patients before Prostatectomy: Evaluation of Potential Chemopreventive Activities. Cancer Prevention Research (Philadelphia, Pa). 2012;5(2):290-8.
44. Potter JD. The failure of cancer chemoprevention. Carcinogenesis. 2014;35(5):974-82.
45. McCaskill-Stevens W, Pearson DC, Kramer BS, Ford LG, Lippman SM. Identifying and Creating the Next Generation of Community-Based Cancer Prevention Studies: Summary of a National Cancer Institute Think Tank. Cancer Prevention Research (Philadelphia, Pa). 2017;10(2):99-107.
46. [Available from: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/aspirin-to-prevent-cardiovascular-disease-and-cancer.
47. Cafferty FH, Coyle C, Rowley S, Berkman L, MacKensie M, Langley RE. Co-enrolment of Participants into Multiple Cancer Trials: Benefits and Challenges. Clinical Oncology. 2017;29:126-33.

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**Table 1.** Baseline characteristics of men randomized

| | Dietary advice n = 44 | | Lycopene capsules n = 44 | | Placebo capsules n = 45 | |
|---|---|---|---|---|---|---|
| | n | Mean (SD) or % | n | Mean (SD) or % | n | Mean (SD) or % |
| Age, y | 44 | 63.3 (4.4) | 44 | 64.0 (5.8) | 45 | 63.1 (4.3) |
| BMI[a], kg/m$^2$ | 18 | 26.9 (4.9) | 23 | 25.5 (2.8) | 20 | 27.7 (3.6) |
| BP[b] systolic, mmHg | 41 | 144 (16) | 43 | 149 (17) | 42 | 141 (17) |
| PSA, ng/mL | | | | | | |
| <3.0 | 20 | 45.5 | 19 | 43.2 | 21 | 46.7 |
| 3.0-19.9 | 22 | 50.0 | 25 | 56.8 | 24 | 53.3 |
| Family history of prostate cancer | 4 | 9.1 | 2 | 4.6 | 5 | 11.1 |
| Total energy intake, kcal/d | 43 | 2240 (582) | 43 | 2265 (643) | 40 | 2291 (486) |
| High alcohol intake[c] | 15 | 34.1 | 15 | 34.1 | 16 | 35.5 |

| | GT drink n= 45 | | Green tea (GT) GT capsules n = 45 | | Placebo capsules n = 43 | |
|---|---|---|---|---|---|---|
| | n | Mean (SD) or % | n | Mean (SD) or % | n | Mean (SD) or % |
| Age, y | 45 | 63.3 (5.4) | 45 | 63.2 (4.0) | 43 | 64.0 (5.1) |
| BMI, kg/m$^2$ | 23 | 25.5 (2.5) | 15 | 27.5 (4.0) | 23 | 27.1 (4.6) |
| BP[a] systolic, mmHg | 42 | 147 (15) | 43 | 144 (16) | 41 | 144 (20) |
| PSA, ng/mL | | | | | | |
| <3.0 | 19 | 42.2 | 22 | 48.9 | 19 | 44.2 |
| 3.0-19.9 | 25 | 55.6 | 23 | 51.5 | 23 | 53.3 |
| Family history of prostate cancer | 4 | 9.1 | 2 | 4.6 | 5 | 11.1 |
| Total energy intake, kcal/d | 41 | 2459 (530) | 44 | 2194 (561) | 41 | 2146 (586) |
| High alcohol intake[b] | 19 | 40.2 | 15 | 33.3 | 12 | 27.9 |

[a]Height from a ProtecT-linked study which around 60% of participants joined.
[b]Blood pressure.
[c]Above 20 units/week (UK male recommendation).

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**Table 2**. Plasma concentrations and dietary intake of lycopene and green tea at baseline and six months

| Intervention: plasma level or dietary intake | Baseline n = 133 | Six months n = 132 | Difference from placebo at six months (95% CI) | p-value |
|---|---|---|---|---|
| **Lycopene** | | | | |
| Plasma lycopene (µmoL/L) | | | | |
| Dietary advice (n = 43) | 0.63 (0.46, 0.98)[a] | 0.82 (0.68, 1.13)[a] | 1.28[c] (1.09, 1.50) | 0.003 |
| Active capsules (n = 42) | 0.67 (0.48, 0.82) | 0.91 (0.72, 1.13) | 1.42 (1.21, 1.66) | <0.001 |
| Placebo capsules (n = 42) | 0.53 (0.43, 0.68) | 0.60 (0.45, 0.78) | - | - |
| Daily intake (mg) | | | | |
| Dietary advice (n = 38) | 2.00 (0.79, 3.56)[a] | 3.26 (1.65, 16.08)[a] | 2.82 (1.94, 4.10) | <0.001 |
| Active capsules (n = 40) | 1.50 (0.60, 2.01) | 1.26 (0.71, 2.16) | 0.99 (0.68, 1.44) | 0.952 |
| Placebo capsules (n= 39) | 1.56 (0.73, 2.14) | 1.33 (0.68, 2.11) | - | - |
| **Green tea (GT)** | | | | |
| Plasma catechins[d] (nM) | | | | |
| GT drink (n = 41) | 0 (0, 1.1)[a] | 24.9 (0, 51.9)[a] | 20.0 (7.0, 32.0)[e] | <0.001[f] |
| Active capsules (n = 45) | 0 (0, 0) | 12.3 (0, 27.5) | 10.7 (0, 19.0) | <0.001 |
| Placebo capsules (n = 41) | 0 (0, 0) | 0 (0, 1.6) | - | - |
| Drinking GT daily | | | | |
| GT drink (n = 38) | 8 (21)[b] | 30 (79)[b] | 0.74 (0.59, 0.88)[g] | <0.001 |
| Active capsules (n = 41) | 5 (12) | 5 (12) | 0.07 (-0.05, 0.19) | 0.279 |
| Placebo capsules (n = 38) | 1 (2) | 2 (5) | - | - |

[a]Median (interquartile range).
[b] Number (percentage).
[c]Ratio of geometric means (active intervention: placebo), adjusted for baseline values.
[d]Green tea catechin (EGCG: epigallocatechin-*O*-glucaronide).
[e]Median difference between active intervention and placebo estimated using generalized Hodges-Lehmann median difference.
[f]p-value estimated using Mann-Whitney test.
[g]Proportion difference (active intervention: placebo) estimated using Two-proportion z-test.

**Table 3.** Men's views about adherence and green tea (GT) and lycopene consumption

| **Men** | **Adherence and experience of the interventions** |
|---|---|
| A | "Well its its straightforward. What I did was I kept them [capsules] in a shredded wheat box [a breakfast cereal] so every morning when I had my shredded wheat I had a couple of tablets" |
| B | "The pill [lycopene capsules], I just had the pill with my breakfast, my first cup of coffee or whatever and the pills were just on the side. I just do it there obviously and so it was quite easy to do that. I don't think I ever dropped out of one of those except when I said I went away and I forgot." |
| C | "No I don't say I particularly like taking tablets [GT capsules] but you know but as it's over a period of time then I don't mind it's not necessarily a problem. Um I take blood pressure tablets anyway so to take one in the morning and one in the evening that's what we had to do it's not a problem." |
| D | "Well, I suppose, initially, they [weekly log] did. After the first month I thought, oh, well, they've got me into the routine now, so I'm okay." |
| E | "Sometimes when you go on holiday, and things like that, obviously your routine changes, so...It's more difficult when you're away, you have to...your meals are being supplied, things like that, and you're not in your environment, so it was a bit more difficult but...Still managed it, still carried on exactly the same, as near as I could…" |
| F | [GT drink]: "Well, I thought it might still be doing me some good…. I think it's that, so I come to enjoy it. So it's just, it's now sort of a way of life" |
| G | "I do yeah I think I yes. I've always eaten a lot of tomatoes in all sorts of different ways and I am now aware of it so because I've upped the intake for 6 months and I've concentrated on that sort of effort because if it's going to be of any help you want to make a good job of it and so its it's in my mind anyway." |
| H | "I saw them [capsules] as a health pill, if you'd have said that they were prescribed drugs you wanted to try maybe I wouldn't have joined, I see a lot of people on blood pressure pills in my age group and I wouldn't like to get on them myself, it's things like that you tend to depend on them eventually." |

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**Table 4:** Adverse effects at six months

| **Adverse symptom in the previous month** | **Dietary advice N=39 min.** | **Lycopene Lycopene capsules N=40 min.** | **Placebo capsules N=41 min.** | **Green tea (GT) GT drink N=40 min.** | **GT capsules N=41 min.** | **Placebo capsules N=39 min.** |
|---|---|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Nocturia | 18 (45) | 14 (34) | 21 (50) | 19 (46) | 21 (50) | 13 (33) |
| Hypertension | 8 (20) | 8 (20) | 6 (14) | 7 (17) | 9 (22) | 6 (15) |
| Insomnia | 8 (20) | 4 (10) | 9 (21) | 9 (22) | 9 (21) | 3 (8) |
| Fatigue | 6 (15) | 3 (7) | 10 (24) | 2 (5) | 10 (24) | 7 (18) |
| Cramp | 7 (18) | 3 (8) | 3 (7) | 6 (15) | 3 (7) | 4 (10) |
| Shortness of breath | 3 (8) | 3 (7) | 4 (10) | 1 (2) | 1 (2) | 8 (20) |
| Heartburn | 3 (8) | 3 (7) | 3 (7) | 3 (7) | 0 (0) | 6 (15) |
| Headache | 1 (3) | 2 (5) | 6 (14) | 1 (2) | 3 (7) | 5 (13) |
| Diarrhoea | 0 (0) | 1 (2) | 3 (7) | 1 (2) | 1 (2) | 2 (5) |

Two participants also reported bad breath (1 in each placebo) and two nausea (1 in lycopene capsules and 1 green tea drink).

**Table 5.** Clinical outcomes at six months

| Intervention and clinical outcome | Baseline n = 133 | Six months n = 132 | Difference from placebo at 6 months (95% CI) | p-value |
|---|---|---|---|---|
| **Lycopene** | | | | |
| PSA (ng/ml) | | | | |
| Dietary advice (n = 38) | 3.1 (2.5, 3.9)[a] | 3.0 (2.3, 4.2)[a] | 0.99 (0.87, 1.11)[c] | 0.817 |
| Active capsules (n = 41) | 3.2 (2.6, 4.5) | 3.2 (2.7, 4.5) | 1.01 (0.89, 1.14) | 0.897 |
| Placebo capsules (n = 42) | 3.0 (2.3, 3.8) | 3.2 (2.4, 4.3) | - | |
| Weight (kg) | | | | |
| Dietary advice (n = 42) | 85.0 (13.7)[b] | 84.8 (14.1)[b] | 0.0 (-2.1, 2.1)[d] | 0.986 |
| Active capsules (n = 38) | 81.8 (11.0) | 81.5 (11.1) | -0.2 (-2.4, 1.9) | 0.821 |
| Placebo capsules (n= 41) | 86.5 (14.7) | 86.2 (14.9) | - | |
| Blood pressure (systolic mmHg) | | | | |
| Dietary advice (n = 40) | 145.2 (15.5)[b] | 143.8 (11.7)[b] | 0.8 (-4.9, 6.4)[d] | 0.786 |
| Active capsules (n = 39) | 148.6 (17.4) | 148.9 (19.3) | 4.2 (-1.5, 9.9) | 0.148 |
| Placebo capsules (n= 42) | 141.3 (17.3) | 141.1 (13.7) | - | |
| **Green tea (GT)** | | | | |
| PSA (ng/ml) | | | | |
| GT drink (n = 39) | 3.1 (2.5, 4.5)[a] | 3.6 (2.4, 4.4)[a] | 1.06 (0.94, 1.20)[c] | 0.357 |
| Active capsules (n = 45) | 3.1 (2.5, 3.7) | 3.1 (2.4, 4.3) | 1.02 (0.91, 1.16) | 0.698 |
| Placebo capsules (n = 37) | 3.2 (2.3, 3.9) | 3.0 (2.3, 4.1) | - | |
| Weight (kg) | | | | |
| GT drink (n = 39) | 82.6 (12.6)[b] | 81.5 (14.1)[b] | -0.8 (-2.9, 1.3)[d] | 0.434 |
| Active capsules (n = 41) | 85.2 (13.4) | 85.5 (12.8) | 0.7 (-1.4, 2.7) | 0.511 |
| Placebo capsules (n = 41) | 85.8 (14.0) | 85.4 (13.7) | - | |
| Blood pressure (systolic mmHg) | | | | |
| Dietary advice (n = 40) | 146.3 (14.8)[b] | 148.1 (16.3)[b] | 3.9 (-2.6, 10.3)[d] | 0.236 |
| Active capsules (n = 41) | 144.9 (16.0) | 142.6 (13.2) | 0.0 (-6.3, 6.4) | 0.998 |
| Placebo capsules (n= 40) | 143.6 (19.7) | 142.9 (16.3) | - | - |

[a]Median (interquartile range).
[b]Mean (standard deviation).
[c]Ratio of geometric means or [d]difference in means between active intervention and placebo, adjusted for baseline values.

**Figure 1**: Consort flow diagram of study participants

**ENROLLMENT**

Eligible and invited (n= 469)

Declined to participate (n =366)
- No reply to invitation (n=146)
- Declined invitation (n=164)
- Did not attend appointment (n=14)
- Other (n=12)

Randomized (n = 133)

**ALLOCATION**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **14** Lycopene dietary advice & GT* drink | **16** Lycopene dietary advice & GT capsules | **14** Lycopene dietary advice & GT placebo | **15** Lycopene capsules & GT drink | **14** Lycopene & GT capsules | **15** Lycopene capsules & GT placebo | **16** GT drink & Lycopene placebo | **15** GT capsules & Lycopene placebo | **14** Lycopene & GT placebo |

**FOLLOW-UP+ & ANALYSIS**

**LYCOPENE**

Lycopene dietary advice (n=44)
**43** Analysed at 6 months
- no baseline blood sample (n=1)

Lycopene capsules (n=44)
**42** Analysed at 6 months
- no follow-up blood sample (n=2)

Lycopene placebo capsules (n=45)
**42** Analysed at 6 months
- no baseline blood sample (n=3)

**GREEN TEA**

GT drink (n=45)
**41** Analysed at 6 months
- no baseline blood sample (n=3)
- no follow-up blood sample (n=1)

GT capsules (n=45)
**45** Analysed at 6 months

GT placebo capsules (n=43)
**41** Analysed at 6 months
- no baseline blood sample (n=1)
- no follow-up blood sample (n=1)

*GT: Green tea, +no participants discontinued intervention.

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