Cancer
Prevention
Research

Randomized, Placebo-Controlled Trial of Green Tea Catechins for Prostate Cancer Prevention

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Abstract

Preclinical, epidemiologic, and prior clinical trial data suggest that green tea catechins (GTC) may reduce prostate cancer risk. We conducted a placebo-controlled, randomized clinical trial of Polyphenon E (PolyE), a proprietary mixture of GTCs, containing 400 mg (−)-epigallocatechin-3-gallate (EGCG) per day, in 97 men with high-grade prostatic intraepithelial neoplasia (HGPIN) and/or atypical small acinar proliferation (ASAP). The primary study endpoint was a comparison of the cumulative one-year prostate cancer rates on the two study arms. No differences in the number of prostate cancer cases were observed: 5 of 49 (PolyE) versus 9 of 48 (placebo), $P = 0.25$. A secondary endpoint comparing the cumulative rate of prostate cancer plus ASAP among men with HGPIN without ASAP at baseline, revealed a decrease in this composite endpoint: 3 of 26 (PolyE) versus 10 of 25 (placebo), $P < 0.024$. This finding was driven by a decrease in ASAP diagnoses on the Poly E (0/26) compared with the placebo arm (5/25). A decrease in serum prostate-specific antigen (PSA) was observed on the PolyE arm [−0.87 ng/mL; 95% confidence intervals (CI), −1.66 to −0.09]. Adverse events related to the study agent did not significantly differ between the two study groups. Daily intake of a standardized, decaffeinated catechin mixture containing 400 mg EGCG per day for 1 year accumulated in plasma and was well tolerated but did not reduce the likelihood of prostate cancer in men with baseline HGPIN or ASAP. *Cancer Prev Res; 8(10); 879–87. ©2015 AACR.*

Introduction

Prostate cancer remains the most common noncutaneous malignancy among men in the United States, despite advances in the treatment of localized and metastatic disease over the past decade (1). The development of prostate cancer is a long-term process driven by genetic and epigenetic changes (2) and characterized by abnormal cell and tissue differentiation (3). Although the natural history of high-grade prostatic intraepithelial neoplasia (HGPIN) is not completely understood, it is considered by many to be a premalignant lesion (4). The frequency of HGPIN (5, 6) and the autopsy prevalence of prostate cancer (7) are similar in populations with widely differing prostate cancer incidence and mortality rates, suggesting an environmental influence on the expression of this disease and the possibility of preventing it through pharmacologic means (8–10). The 5-alpha-reductase inhibitors, finasteride and dutasteride, which block the conversion of testosterone to dihydrotestosterone, have been evaluated for prostate cancer chemoprevention in large, phase III chemoprevention trials (11–13). Although these agents significantly reduced the risk of prostate cancer, their use was also associated with increased detection of high-grade disease, severely limiting their clinical adoption and underscoring the need to identify novel prostate cancer prevention agents (12).

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Green tea catechins (GTC) influence proliferation, apoptosis, and other hallmarks of carcinogenesis with an acceptable safety profile, making them attractive candidates for chemoprevention (14). Twenty percent of green tea is consumed in Asian countries where prostate cancer mortality rates are among the lowest in the world (15) and the risk of prostate cancer appears to be increased among Asian men who abandon their original dietary habits upon migrating to the United States (15). However, case–control and cohort studies addressing the relationship between GTC consumption and prostate cancer risk have been mixed (16, 17).

(GTCs) include (−)-epigallocatechin-3-gallate (EGCG), (−)-epicatechin (EC), (−)-epigallocatechin (EGC), and (−)-epicatechin-3-gallate (ECG). Among these compounds, laboratory studies have identified EGCG as the most potent modulator of molecular pathways thought to be relevant to prostate carcinogenesis (14, 16–19). Preclinical studies of GTCs (20–23) have shown significant reductions in tumor size and multiplicity in the prostate cancer TRAMP mouse model, as well as potent and selective proapoptotic activity in prostate cancer cell lines (16, 18–23). Phase I/II studies (24–30) have demonstrated good bioavailability and tolerability at doses ranging from 200 to 1200 mg EGCG per day. Bettuzzi and colleagues reported a significant reduction in prostate cancer in men with HGPIN randomized to receive one-year of EGCG (24, 25). However, nearly all of the prostate cancer risk-reduction in that study occurred at the 6-month biopsy, suggesting that the results may have been biased by a non-random distribution of occult prostate cancer at baseline. To further explore the potential role of GTCs for prostate cancer chemoprevention, we conducted a randomized, double-blind, placebo-controlled trial of PolyE, a standardized formulation of GTCs containing 400 mg EGCG per day, in men with HGPIN and/or atypical small acinar proliferation (ASAP).

Materials and Methods

The study and the consent procedures were approved by the Institutional Review Boards of all participating institutions. A consort diagram depicting the number of subjects screened, enrolled, randomized, and completed intervention is shown in Fig. 1.

Eligibility and recruitment

Men between age 30 years and 80 years with a biopsy-proven diagnosis of HGPIN and/or ASAP less than 3 months before randomization, with no history of cancer, hepatic or renal disease, restricted from taking steroid or other supplements, or more than 6 to 12 cups of green tea a day, were eligible. The original plan was to include only men with HGPIN. However, to expedite accrual, we expanded the inclusion criteria to also include men with ASAP, as this diagnosis has also been associated with prostate cancer risk. All prostate biopsies were reviewed by a central pathology laboratory and all pathologists were unaware of the treatment-group assignment. Discordant interpretations were arbitrated by a referee pathologist (senior
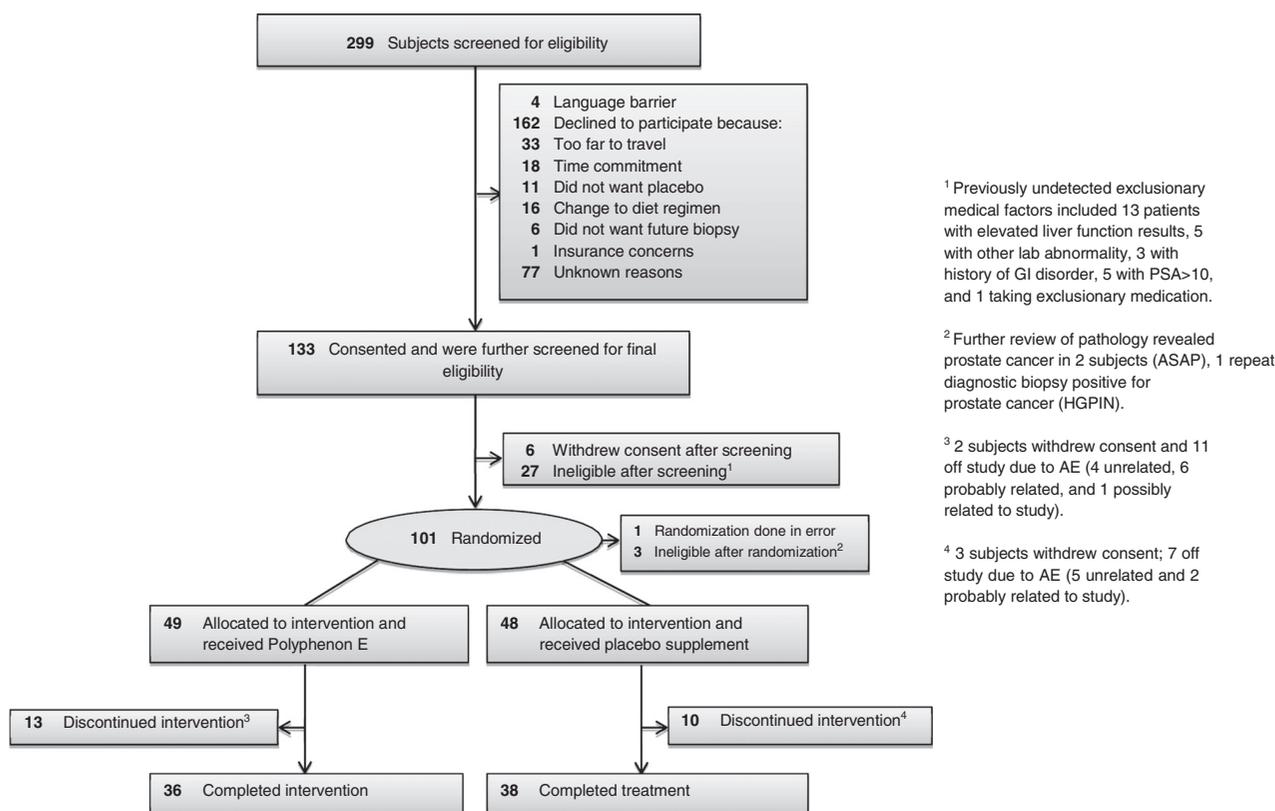

Figure 1.
Consort diagram.

Table 1. Demographic characteristics of all study participants randomized to the clinical trial ($N = 97$)

Variables	Levels	Poly E ($N = 49$) N (%)	Placebo ($N = 48$) N (%)	P^a
Age, y	Mean (SD)	62.0 (7.9)	64.1 (7.9)	0.24
Race	Black or African American	8 (16.3)	12 (25.0)	
	White	41 (83.7)	36 (75.0)	0.32
Ethnicity	Hispanic	6 (12.2)	3 (6.3)	
	Non-Hispanic	42 (85.7)	45 (93.8)	
	Unknown	1 (2.0)	0 (0.0)	0.40
Family history of prostate cancer	N	42 (85.7)	45 (93.8)	
	Y	7 (14.3)	3 (6.3)	0.32
Body mass index (weight in Kgs/height in m^2)	Mean (SD)	29.6 (4.9)	29.8 (4.9)	0.91
PSA (ng/mL)	Mean (SD)	4.5 (1.8)	4.6 (2.1)	0.67
Subjects with baseline HGPIN		32 (65.3)	34 (70.8)	0.66
No. of cores with baseline HGPIN	Mean (SD)	1.8 (1.4)	2 (1.1)	0.13
Subjects with baseline ASAP		17 (34.7)	14 (29.2)	0.66
No. of cores with baseline ASAP	Mean (SD)	1.3 (0.6)	1.5 (0.8)	0.44

[a]P values were computed by Fisher exact test for categorical variables, Wilcoxon rank-sum test for continuous variables.

pathologist at Moffitt Cancer Center), and concordance was achieved in all cases. Participants were enrolled at the Moffitt Cancer Center, James A. Haley VA Hospital, Tampa and University of Florida, Jacksonville, Florida from September 2008 to March 2013. Less than 5% of subjects were recruited from other sites. Potential participants were identified by the primary surgeon and invited for eligibility screening. Screened subjects were recruited to a run-in period where a 10-day supply of multivitamin/mineral supplements, food intake, and symptom logs was provided, designed to assure compliance with supplement intake and maintenance of the required study logs. Confirmation of diagnosis by central pathology review, ≥85% compliance to instructions during the run-in period, review and confirmation of inclusion and exclusion criteria and normal laboratory results were required for randomization.

Randomization and blinding

After eligibility was confirmed and consent obtained, participants were assigned to the intervention or placebo arm (1:1) using the SRAR system, a web-delivered subject registration application, stratified by diagnosis (HGPIN or ASAP). All study staff and participants, with the exception of the clinical pharmacist and biostatistician, were blinded to the assignments until the completion of the trial. At randomization, baseline assessments of lower urinary tract symptoms (LUTS) using the LUTS Symptoms Scale, (31), quality of life (QOL), using the Rand Short-form (SF)-36 (32), PSA, and plasma catechin levels were obtained. Blood samples, urine, and tissue from diagnostic biopsy were collected for baseline measurements and banked for future studies.

Intervention

Polyphenon E (PolyE), an investigational agent manufactured by Mitsui Norin Co., Ltd., was used in this clinical trial. The active pharmaceutical ingredient of PolyE is a purified tea fraction containing 80% to 98% total catechins by weight, the main component of which is EGCG, comprising 50% to 75% of the material. PolyE contains minimal amounts of caffeine, (<1.0%) theobromine (<1.0%), and gallic acid (<0.5%). The investigational product used in this study was a hard gelatin formulation containing 200 mg EGCG/capsule. PolyE and matching placebo capsules were manufactured under contract to NCI, DCP in

compliance with current good manufacturing practice regulations. An investigator-initiated IND (77626 Kumar NB PI) was obtained for this agent at this dose and for this indication. Periodical testing was conducted to ensure drug stability with full potency of agent documented until March 2014. To minimize the use of other supplements, a standard vitamin and mineral formulation containing 100% U.S. recommended daily allowance was provided to all participants for the duration of the study.

Participant follow-up

LUTS (31), QOL (32), plasma catechin levels, PSA, and nutritional intake data were evaluated at baseline, 3 and 6 months, and at end-of-study (EOS). Monthly assessments of toxicity (CTCAE 4.0), concomitant medications and organ function, including hepatic panel, PT/PTT, and LDH, were performed. Repeat biopsies were performed at 6 months for (a) PSA velocity >0.75 ng/mL or (b) documentation of a prostate nodule on digital rectal examination. All participants who did not have prostate cancer detected on an interim biopsy underwent EOS biopsy at 1 year. Any toxicities (adverse events) occurring during the study were reviewed by the treating physician and managed according to standard medical practice. The intervention was terminated if a participant developed prostate cancer or a serious adverse event. All subjects were contacted 7 ± 3 days following the 1-year intervention to assess toxicity and concomitant medications.

Adherence

Compliance with study agent intake was measured during monthly visits via pill counts and self-reported daily study-agent intake logs. Adherence was assessed by measuring plasma catechin levels at baseline, 6 months, and EOS. A validated liquid chromatography triple quadrupole mass spectrometry (LC/MS-MS) method (Thermo Scientific) was used to determine plasma catechin levels. We were able to successfully quantitate the four catechins (EGCG, EGC, ECG, and EC) using methods previously described (26, 33, 34).

Study end points

The primary endpoint was a comparison of the cumulative number of prostate cancer diagnoses at 1-year on the two study arms. As a prespecified secondary endpoint, we also compared the cumulative rate of prostate cancer plus ASAP at 1-year among the

Table 2. Diagnosis of prostate cancer by treatment arm of men with baseline diagnosis of HGPIN and ASAP (N = 97)

Treatment	Total subjects	Censored[b] due to AE before 6 mo (N)	Prostate cancer at 6 mo (N)	Censored[b] due to AE between 6 and 12 mo (N)	Prostate cancer at 12 mo (N)	Censored[b] at 12 mo (N)	Total prostate cancer events	Log-rank P[a]
Placebo	48	12	3	1	6	26	9	
Polyphenon E	49	14	1	1	4	29	5	0.25
Total	97	26	4	2	10	55	14	

[a]The log-rank test is an overall comparison on the diagnosis of prostate cancer, as a time-to-event endpoint.
[b]Censored patients due to AEs.

men with HGPIN without ASAP at baseline (Clinical Trials.gov NCT00596011). Additional secondary endpoints included comparisons of treatment-related adverse events (AE) and the effect of PolyE on serum PSA values from baseline to 6 and 12 months.

Data management and study monitoring

All collected data were entered from source documents or case report forms (CRF's) directly into the web-based ONCORE system at each site by authorized, trained staff. Toxicities were monitored continuously through the trial by the PI and study physician at each site. The study was monitored in accordance with the Protocol Review and Monitoring System at the Moffitt Cancer Center and an External Data and Safety Monitoring Board (EDSMB).

Statistical analysis

The original assumptions for the statistical power calculations for this study were derived from the trial by Bettuzzi and colleagues (24, 25) in which only one prostate cancer was diagnosed among 30 men on the GTC arm (1/30;3%) at 1 year compared with nine in the placebo arm (9/30;30%), suggesting a 90% chemoprevention efficacy for this intervention in men with HGPIN. On the basis of prior reports of prostate cancer rates among men with HGPIN (20%; refs. 8, 35, 36) and ASAP (40%; refs. 8, 37, 38), we anticipated that the overall one-year rate of prostate cancer on the placebo arm would be 30%. This study had 79% power (two-sided) to detect a change from 30% to 9% with 50 patients per arm (derived from PASS 2008); with a power of 98% if the true rate of progression was 0.03 in the better group and 0.30 in the inferior group. The overall rate of prostate cancer diagnoses among men with HGPIN or ASAP on baseline biopsy in the two treatment groups was compared using the log-rank test, with event times at either 6 or 12 months. A prespecified secondary endpoint comparing the cumulative 1-year rate of prostate cancer plus ASAP among men with HGPIN without ASAP at baseline was performed using the Barnard unconditional test, as no cases of prostate cancer were detected before the 12 month EOS biopsy in this group. An intention-to-treat analysis was used for the primary efficacy endpoint. Baseline participant characteristics were compared between the two groups using Fisher exact tests for categorical variables and Wilcoxon rank-sum test for continuous

variables. Trend for adverse events by group, grade, and causality were compared using the Jonckheere–Terpstra test and toxicity symptoms using the Barnard unconditional test. Plasma EGCG levels, nutritional intake, LUTS, and QOL were compared by study arm from baseline to end of intervention using two-sided Wilcoxon rank-sum test. We estimated the overall treatment effect on serum PSA between the two arms using the GEE model which accounts for all 74 patients with PSA values at 6 and 12 months. To assess the effect of treatment on prostate cancer grade in subjects who developed prostate cancer while on study, we compared Gleason categories using a Fisher exact test at $\alpha = 0.05$ for the 2×4 contingency table.

Results

Of a total of 299 men meeting all eligibility requirements, 97 were randomized on study (Fig. 1). Forty-nine participants were randomized to the PolyE arm and 48 to the placebo arm, with 70 completing the 12-month intervention and 74 reaching the primary endpoint, with at least a 6-month biopsy. Table 1 displays the baseline characteristics of all study participants. The two study arms were well matched for potential predictive markers, including age, race, PSA, number of positive cores, and body mass index (BMI).

The primary endpoint of this study was not met as significant differences in prostate cancer rates were not observed between the two study arms: 5 of 49 (10.2%) Poly E versus 9 of 48 (18.8%) placebo, $P = 0.25$ (Table 2). However, in a prespecified secondary analysis performed in men with HGPIN without ASAP at baseline, a decrease in the composite endpoint of prostate cancer plus ASAP was observed for the PolyE arm (3/26 PolyE vs. 10/25 placebo, $P < 0.024$). In addition, fewer men with HGPIN without ASAP at baseline were subsequently diagnosed with ASAP on the PolyE (0/26) than on the placebo arm (5/25; Table 3). In this subgroup of men with HGPIN-only at baseline, no subjects met the criteria for biopsy at 6 months in either the PolyE or placebo arm. Among the men with ASAP at baseline, 2 of 17 in the PolyE arm versus 4 of 14 in the placebo arm were subsequently diagnosed with prostate cancer over the 12-month study. Among the 10 cancers diagnosed on the 12-month biopsy, no significant effect of the intervention on tumor grade could be

Table 3. Combined rate of prostate cancer + ASAP at 12 months in a subgroup of men with baseline HGPIN without ASAP (N = 51)

| Treatment	Total subjects (N)	ASAP or prostate cancer at 6 months (N)	ASAP at 12 mo (N)	Prostate cancer at 12 mo (N)	Combined rate of ASAP + prostate cancer at 12 months (N)	P[a]
Placebo	25	0	5	5	10	
Polyphenon E	26	0	0	3	3	0.024
Total	51	0	5	8	13	

[a]Barnard unconditional test.

Table 4. Summary of toxicities by final attribution and treatment arm—all patients (N = 97)

Final attribution	Treatment arms		
N (%)	Placebo	Polyphenon E	Total
Definite	0 (0)	0 (0)	0 (0)
Possible	3 (1.78)	7 (3.30)	10 (2.62)
Probable	1 (0.59)	5 (2.36)	6 (1.57)
Unlikely	9 (5.33)	7 (3.30)	16 (4.20)
Unrelated	156 (92.31)	193 (91.04)	349 (91.60)
Total	169 (44.36)	212 (55.64)	381 (100.0)

detected. No significant differences between the treatment and placebo arms were observed in LUTS and QOL scores from baseline to end of study (data not shown).

A summary of all toxicities by final attribution appears in Table 4. There were more possible and probable events in the treatment arm compared with the placebo, all but one of which was grade I or II. One participant on the PolyE arm had grade III nausea possibly related to study agent. On the basis of the directive from FDA, 11 (11) subjects met off-study criteria due to AEs in the treatment arm compared with seven (7) in the placebo arm (data not shown). The number of subjects who met FDA-imposed off-study criteria due to grade I-II toxicity related to LFTs was not significantly different between the two groups. Both PolyE and the matching placebo used in the trial were hard gelatin capsules with no difference in appearance, taste, or smell and subject to periodical testing to ensure drug stability, potency, and other attributes of the study agent. Because Poly E was caffeine-free, there were no differences in patient-reported caffeine-related or other symptoms. Although grade I–II toxicities were more frequently observed in the PolyE arm, these were determined from monthly CMP panels and not subject-reported symptoms. Subjects and study staff were thus unable to guess group assignment based on reported symptoms, ensuring successful double blinding. Adherence to agent/placebo was greater than 90% as indicated by pill count, self-reported agent logs, and plasma catechin levels.

A significantly greater number of subjects in the treatment arm had an increase in plasma catechin EGCG concentra-
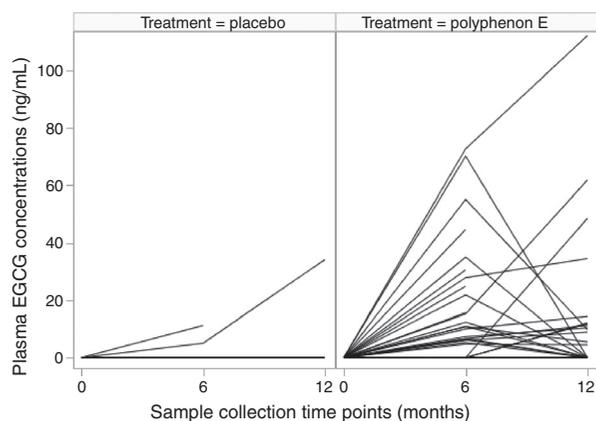
*Most subjects in the placebo arm had non-detectable plasma EGCG concentrations at each time point.

Figure 2.
Change in individual plasma EGCG concentrations at baseline, 6 and 12 months by treatment arm. Most subjects in the placebo arm had nondetectable plasma EGCG concentrations at each time point.

tions at 6 and 12 months ($P < 0.0001$ and $P = 0.0002$, respectively; Table 5). Greater individual change in plasma concentrations of EGCG was observed in the treatment arm at 6 and 12 months (Fig. 2) in the PolyE arm compared with placebo. Although compliance was verified by pill counts and diaries, individual EGCG concentrations decreased in the second half of the year in the PolyE arm. Other catechins were nondetectable or below quantifiable levels in the plasma of all subjects. No significant change in intake of specific nutrients from baseline to the end of study was observed, indicating that compliance was maintained on both study arms (data not shown).

A comparison of the estimated overall treatment effect showed a greater reduction of serum PSA in men on the PolyE arm (−0.87 ng/mL; 95% CI, −1.66–−0.09; Table 6). No effect on PSA was observed among the 14 men in whom prostate cancer was diagnosed during the study.

Table 5. Plasma concentrations of EGCG from baseline to postintervention by study arm (N = 74)

	Placebo				Polyphenon E				
Time (mo)	N (EGCG>0)	25% Quartile ng/mL	Median ng/mL	75% Quartile ng/mL	N (EGCG>0)	25% Quartile ng/mL	Median ng/mL	75% Quartile ng/mL	P^a
0	0/38	0	0	0	0/36	0	0	0	1
6	2/37	0	0	0	22/35	0	6.6	21.8	<0.0001
12	1/31	0	0	0	13/28	0	0	11.5	0.0002

[a]P value comparing all individual patients' plasma EGCG concentrations at each time point between placebo vs. poly E was calculated from the Wilcoxon rank-sum test, two sided.

Table 6. GEE model of change in Serum PSA (ng/mL) from baseline to postintervention by study arm (N = 74)

Treatment	Time (mo)	N	25% Quartile ng/mL	Median ng/mL	75% Quartile ng/mL	Treatment effect on overall PSA change[a]	P^a
Placebo	0	37	3.70	4.80	6.10		
	6	36	3.55	5.45	6.30		
	12	28	3.65	4.90	6.15	−0.87 ng/mL (95% CI, −1.66 to −0.09)	0.029
Polyphenon E	0	36	3.50	4.45	5.60		
	6	35	2.80	3.70	5.20		
	12	29	2.80	3.50	5.10		

[a]The P value and overall serum PSA change from GEE model accounts for all values at 6 and 12 months, and estimates an overall treatment effect during the study.

Discussion

In this phase II, randomized, placebo-controlled trial of PolyE in men with HGPIN and/or ASAP, no significant differences in prostate cancer rates between the two study arms were observed at one year. Although PolyE was associated with a decrease in the composite endpoint (prostate cancer plus ASAP), that finding was largely driven by the absence of ASAP on EOS biopsies on the PolyE arm. ASAP is an entity that reflects a broad group of lesions of varying clinical significance with insufficient cytologic or architectural atypia to establish a definitive diagnosis of prostate cancer (8, 38). To date, there is no clear evidence that HGPIN and ASAP represent steps on a linear path to prostate cancer. Consequently, these findings should be interpreted with caution.

Notably, only 6 of 31 men with baseline ASAP were subsequently diagnosed with prostate cancer during this one-year study. Previous reports of cancer detection rates within one year of a diagnosis of ASAP have ranged from 40% (8) to 59.1% (37–39) depending on the number of cores sampled on the diagnostic and follow-up biopsies, suggesting that this diagnosis may reflect a poorly sampled prostate cancer (40–43). Our requirement of at least 8 cores on the diagnostic biopsy may explain the relatively low rates of cancer detected on subsequent biopsies in patients with ASAP in this study.

As our power calculation assumptions were based on a higher incidence of prostate cancer on the placebo arm than was ultimately observed (30% vs. 18.8%), and as only 65% of our participants had HGPIN at baseline (53% with HGPIN-only and 12% with HGPIN + ASAP), this study did not have sufficient power to detect small differences in prostate cancer rates in the HGPIN cohort. However, these data are in sharp contrast with the large effect size suggested by Bettuzzi and colleagues, who reported a 90% reduction in prostate cancer among men with HGPIN randomized to receive GTCs for one year. As noted above, the fact that nearly all of the benefit in that study occurred by 6 months suggests that sampling error may have contributed to their findings (24, 25).

The PolyE dose and administration guidelines, for example, required to be taken with food, were selected to minimize toxicity. Although the tolerability of EGCG at doses of up to 1,200 mg/day (24–26, 33, 34, 44, 45) has been well documented, legitimate concerns persisted regarding the safety of prolonged administration. Increased oral bioavailability occurs when GTCs are consumed in a fasting state (34) and increased toxicity, including hepatotoxicity had been reported in animal studies (46, 47) and in anecdotal reports in humans (48–50). Therefore, the FDA restricted the PolyE dosage to 200 mg BID EGCG and required that it be taken with food. Because of reports of liver toxicity in clinical and preclinical trials (46–50), the FDA also required that a liver panel be obtained at baseline and every 4 weeks during treatment. Following any elevation in alanine transferase, the study drug was withheld (grade 1) or discontinued (grade 2), and serum enzymes monitored until recovery to normal.

A significant increase in plasma EGCG concentration was achieved in the treatment arm at 6 and 12 months, although mean plasma EGCG concentrations (6 months: 14.7 ng/mL SD:19.9 and 12 months: 12.3 ng/mL SD:24.8) were lower than that reported in previous phase I trials (34, 45). Nguyen and colleagues (45) reported plasma EGCG concentrations of 68.8 ng/mL after 3 to 6 weeks of PolyE (dosed at 800 mg EGCG per day) during the pre-prostatectomy period. Notably, catechin levels in prostate tissue were low to undetectable following the short-term administration of PolyE in that study, raising questions about the plausibility that this agent could have an effect at the tissue level. Studies on single doses in fasting and fed conditions using 400, 800, and 1,200 mg EGCG per day have reported higher plasma EGCG concentrations in fasting conditions relative to fed conditions. Studies using varying doses (400 mg, 800 mg EGCG) of GTCs and PolyE administered in single and repeated dosing schedules for 4 weeks have reported maximum concentrations of EGCG levels 390.3 6 ng/mL and 287.6 ng/mL (800 mg EGCG) and 161.4 and 155.4 ng/mL (400 mg EGCG), respectively (33). On the other hand, Lee and colleagues reported much lower peak plasma concentrations of EGCG [34.72 ng/mL (SD 22.87)] compared with others with a single administration of 2 mg EGCG/kg body weight (51). In addition, similar to previous observations (33, 34, 45), not all subjects in the treatment arm had detectable levels of EGCG. Although instructed to take the dose of PolyE within 4 hours of the blood draw, with travel time and scheduling challenges, these subjects may have not complied with these instructions. In addition, individual variation in absorption cannot be discounted.

The value of PSA changes in a chemoprevention setting is debatable. Despite this drawback, serum PSA as a continuous variable has been widely used in prostate cancer chemoprevention trials (52–54) as well as in clinical practice, where PSA levels are used to define risk categories (37, 55–57). In contrast with prior reports (25, 45), PolyE was associated with a decrease in serum PSA in the current trial. However, among the 14 men who were diagnosed with prostate cancer during the study, a significant decrease in PSA was not observed. Although the mechanism(s) that could explain the PSA reduction are unclear, there is emerging evidence from epidemiologic, histopathological, and molecular pathologic studies that inflammation plays role in the etiology of prostate cancer (58–60). It is, therefore, tempting to speculate that the reduction in serum PSA with GTCs could be due to reduced inflammation. However, several challenges remain about the inflammation hypothesis, including the determination of the cause(s) of chronic inflammation in the prostate and whether inflammation plays a causative role in prostate carcinogenesis (58–60).

LUTS represents a common conglomeration of storage, voiding, and post-micturition symptoms with potentially debilitating effects on quality of life (31, 61, 62). Studies have demonstrated an increased prevalence of LUTS in men over the age of 60 years and in those with benign prostatic hyperplasia (BPH; refs. 31, 61, 62). We were not able to evaluate the effect of PolyE on LUTS as the study participants were generally asymptomatic at baseline.

Randomized chemoprevention trials using agents similar to readily available over-the-counter supplements present unique challenges to recruitment and retention (63). Although several infrastructure, protocol-related, and personal factors were taken into consideration while designing the clinical trial, safety monitoring imposed by the FDA continued to challenge recruitment and retention. Only 33% of an eligible pool of 299 men were ultimately randomized on-study: 162 were unwilling to comply with protocol requirements and 77 refused to participate for unknown reasons. Although those men were unwilling to document their reason for not participating, stringent protocol requirements requiring monthly

blood draws was a contributing factor. Similarly, the completion rate of this one-year intervention was only 76% (74/98), much lower than other chemoprevention trials (11–13, 24, 25). The low completion rate was related to FDA-imposed early stopping rules for grade I–II toxicity. Although attention to safety is critical in developing interventions targeting healthy populations, imposing safety requirements typical of cancer treatment trials can undermine chemoprevention agent development efforts, especially when the concerns are derived from animal studies and case reports of adverse events associated with significantly higher doses than those being proposed.

The strengths of our study include the randomized, placebo-controlled, double-blinded design, the use of a standardized agent, prior clinical, as well as preclinical and epidemiologic evidence of potential efficacy, the relatively long, one-year study duration and the use of a clinically relevant endpoint, prostate cancer, as the primary study objective. The study was guided by an FDA IND, with stringent eligibility criteria, frequent and extensive toxicity monitoring, and early stopping rules for all grades of toxicity and was conducted with the same rigor by which most therapeutic agents are evaluated. Although these factors contributed to the rigor of the study design and conduct, they adversely affected accrual and study completion rates. In addition, as the rate of prostate cancer in our placebo group was lower than expected, and given that only about half of the study participants had HGPIN at baseline, our study was ultimately underpowered to detect small reductions in prostate cancer rates with GTCs in men with HGPIN.

Conclusion

Daily intake of a standardized catechin mixture containing EGCG, 200 mg BID, for one year, accumulated in plasma and was well tolerated but did not reduce the likelihood of a subsequent prostate cancer diagnosis in men with baseline HGPIN or ASAP. Our study confirmed the observations of Epstein (8) and others (53, 54) that the risk of prostate cancer on biopsy within one year following a diagnosis of HGPIN is only about 20% if good sampling is initially performed. In addition, the very low one-year rate of prostate cancer observed in men with ASAP in this trial suggests that earlier reports may have overestimated the true risk of cancer in that cohort, possibly due to poor initial sampling. Apart from meticulously selecting promising agents, validated biomarkers and study endpoints, future prostate cancer chemoprevention trials should ideally enroll larger cohorts of men at higher risk for this disease, perhaps with durations of interventions that continue beyond one year.

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