Results of a phase II randomized, double-blind, placebo-controlled trial of Polyphenon E in women with persistent high-risk HPV infection and low-grade cervical intraepithelial neoplasia ☆

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HIGHLIGHTS

- We conducted the largest randomized trial of a green tea extract for HPV cervical disease.
- Results show that Polyphenon E is acceptable, safe and well tolerated.
- Polyphenon E was not shown to promote the resolution of persistent high-risk HPV.

ARTICLE INFO

ABSTRACT

Objective. In vitro data and pilot data suggest that green tea catechins may possess chemopreventive activity for cervical cancer and precursor lesions. We conducted a randomized, double-blind, placebo-controlled trial of Polyphenon E (decaffeinated and enriched green tea catechin extract) in women with persistent human papillomavirus (HPV) infection and low-grade cervical intraepithelial neoplasia (CIN1) to evaluate the potential of Polyphenon E for cervical cancer prevention.

Methods. Ninety-eight eligible women were randomized to receive either Polyphenon E (containing 800 mg epigallocatechin gallate) or placebo once daily for 4 months. The primary study outcome was oncogenic HPV clearance and clearance of CIN1.

Results. Polyphenon E was shown to be acceptable, safe and well tolerated. There was no difference in the response rate by treatment allocation. Complete response, defined as negative for high-risk HPV and normal histopathology, was noted in 7 (17.1%) and 6 (14.6%) women in the Polyphenon E and placebo arms, respectively. Progression, defined as persistent oncogenic HPV with histopathologic evidence of progression, was more common in the Polyphenon E group than in the placebo group [6 (14.6%) vs. 3 (7.7%)].

Conclusion. Based on the largest randomized placebo-controlled trial of a green tea extract for HPV related cervical disease, we conclude that 4 months of Polyphenon E intervention did not promote the clearance of persistent high-risk HPV and related CIN1. Further studies may be necessary to better delineate the risk factors for persistent HPV infection and biology of the disease to facilitate the evaluation of chemopreventive strategies.

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1. Introduction

Cervical cancer is the most common gynecologic malignancy in women worldwide with an estimated annual incidence of 470,000 cases [1]. Persistent high-risk human papillomavirus (HPV) infection is a requisite precursor to the development of nearly all (>99%) of premalignant (high-grade cervical intraepithelial neoplasia) and invasive carcinomas of the cervix. The recent introduction of virus-like particle prophylactic HPV vaccination provides an effective primary prevention strategy for squamous and adenomatous malignancies of the cervix.

Prophylactic vaccines however are type-specific (16/18 and 16/18/6/11, respectively) and relatively expensive making them inaccessible to many domestic and developing world underserved populations. Although recent encouraging results from the National Health and Nutrition Examination Survey (NHANES) indicate that within 4 years of HPV vaccination introduction there has been a 56% decrease in vaccine-type HPV prevalence among females aged 14–19 years[2], there has not been a decrease in HPV prevalence among older age groups, and current bivalent and quadrivalent prophylactic type restricted vaccines leave nearly a third of high-risk oncogenic strains without a viable primary prevention strategy. A range of non-surgical treatments have been evaluated for the treatment of cervical cancer precursor lesions and prevention of cervical cancer, but the results of these studies have been clinically inconclusive and/or have been associated with safety concerns.

In vitro studies have suggested that green tea catechins may exert chemopreventive activity for cervical cancer. We have shown that epigallocatechin gallate (EGCG, a major green tea catechin) and Polyphenon E (a decaffeinated, enriched, and defined mixture of green tea catechins) inhibited the growth of HPV-positive cervical cancer cells and HPV-immortalized cervical epithelial cells in a dose dependent fashion [3]. Induction of apoptosis and cell cycle arrest was observed in EGCG and Polyphenon E treated cells. Apoptosis-related proteins, p53 and p21 showed dose dependent increase while p27 was not affected. HPV-E7 protein expression was decreased with green tea catechin treatment. In addition, green tea catechins or EGCG has been shown to inhibit epidermal growth factor receptor activation [4], telomerase activity [5], phosphatidylinosital 3-kinase/Akt and extracellular signal-regulated kinase 1/2 signaling pathways [6] in HR HPV immortalized cervical epithelial cells or cervical cancer cells which lead to growth cession.

Preliminary clinical efficacy of green tea extracts (Polyphenon E or EGCG) in patients with HPV infected cervical lesions has been reported [7]. Fifty-one patients with various degrees of cervical dysplasia (mild, moderate, and severe) were divided to receive oral Polyphenon E capsules (containing 200 mg EGCG), EGCG capsules (200 mg), vaginal Polyphenon E ointment, or a combination of oral and vaginal Polyphenon E. Following 8 to 12 weeks of intervention, 23 of 33 subjects receiving either oral or vaginal Polyphenon E demonstrated regression of cervical dysplasia, with a trend toward clearance of HPV. Clinical efficacy of topical sinecatechins, a defined green tea extract, in the treatment of external genital and perianal warts has been documented and topical green tea therapy is now commercially available for treatment of condyloma.[8]

Based on these preliminary findings, we conducted a randomized, double-blind, placebo-controlled clinical trial of oral Polyphenon E in women with persistent high-risk HPV (HR HPV) infection and concomitant low-grade cervical intraepithelial neoplasia (CIN1) to evaluate the potentials of Polyphenon E for cervical cancer prevention. We hypothesized that oral Polyphenon E intervention would induce the histologic regression of CIN1 by promoting the clearance on oncogenic HPV.

2. Materials and methods

2.1. Study drugs

Polyphenon E contains 85%–95% total catechins, with 56%–72% as EGCG. The agent was provided to the National Cancer Institute (IND number 58,367), Division of Cancer Prevention (NCI, DCP) by Mitsui Norin. This study used Polyphenon E oral capsules, standardized to contain 200 mg EGCG per capsule, and matched placebo capsules, supplied by NCI, DCP. Study capsules were stored at room temperature and protected from environmental extremes.

2.2. Study population

The study was conducted primarily at the University of Arizona (Tucson, Arizona), with additional accrual at Maricopa Integrated Health System (Phoenix, Arizona), and Southern Pines Women's Health Center (Southern Pines, North Carolina). All potential participants were identified by participating community clinicians, who provided documentation of HPV, and/or cytology. In cases where oncogenic HPV status was unknown, specimens were collected to establish baseline HPV status during the pre-screening phase of the trial. Participants were required to be at least 18 years of age, had normal liver and kidney function, and good performance status. To be eligible subjects were required to be positive for HR HPV by DNA hybrid capture and have at least one biopsy with histologically documented low-grade cervical intraepithelial neoplasia (CIN) at the time of enrollment. To document persistence prior to enrollment, eligibility also required (6 to 12 months prior) a positive HR HPV on DNA hybrid capture and either LSIL cytology or histologically documented CIN1 on cervical biopsy.

Participants were excluded if they were pregnant or breast feeding, consumed tea regularly within 1 month of enrollment, had a history of allergic reaction to tea or related dietary projects, had been treated for genital condyloma within 30 days of enrollment, were receiving other investigational agents, had prior pelvic irradiation, were HIV positive, had uncontrolled inter-current illness, had invasive or high-grade intraepithelial neoplasia, or had a history of cancer except non-melanoma skin cancer. The study was approved by the institutional review boards of the University of Arizona as well as the collaborating institutions. Written informed consent in English or Spanish was obtained from all participants.

2.3. Study procedures

During the initial visit, participants underwent eligibility evaluation. Baseline HPV, cytology and histopathology data were reviewed as part of eligibility determination. Each participant underwent an interview and a brief physical exam to document medical history, performance status, height, weight, blood pressure, pulse, and temperature measurements. Blood samples were collected for complete blood count with differentials and blood chemistry panel. A urine sample was collected for urine pregnancy test. Participants also underwent baseline colposcopy to confirm the presence of an evaluable low-grade CIN lesion occupying at least 1 quadrant and to exclude the presence of a concurrent high-grade CIN. Colposcopic biopsy with endocervical curettage was obtained if not performed within 90 days prior to enrollment. Specimens were collected for cervical cytology and HR HPV testing.

Upon determination of eligibility, participants were randomized to receive Polyphenon E or placebo. An adaptive allocation randomization procedure was implemented [9] to balance the two groups on the basis of age. Participants were instructed to take 4 study capsules each morning with food for 4 months. Participants returned to the clinic every month for the following procedures: urine collection for pregnancy test, assessment of adverse events, compliance verification with review of drug diary and pill count, and blood collection for hepatic panel.

At the end of the 4-month intervention, blood samples were collected for complete blood count with differentials and blood chemistry panel. A urine sample was collected for urine pregnancy test. All participants underwent a standardized post-intervention colposcopic evaluation with collection of endocervical curettage and collection of specimens for cervical cytology and HR HPV testing. This included biopsy of all clinically visible lesions as well as random biopsies of three of four quadrants when no lesions were visible. All histopathology specimens were reviewed in a blinded fashion by an experienced gynecologic pathologist and were subjected to a second quality control review.

The primary study outcome was HR HPV clearance and resolution of the low-grade CIN at month 4. HR HPV status was determined using DNA hybrid capture testing using the high-risk oncogenic probe (HC2, Hologic, Lexington Massachusetts) and performed by a commercial laboratory. Resolution of low-grade CIN was based on evaluation of cervical cytology and biopsy/endocervical curettage obtained at month 4. This

time frame was selected due to safety considerations and the desire to avoid disease progression.

The following criteria were established a priori for the assessment of the study outcomes: Complete Response (CR) — clearance of HR HPV and complete colposcopic, histologic and cytologic resolution of disease; Partial Response (PR) — clearance of HR HPV with evidence of CIN1 on cervical biopsy, endocervical curettage, or ASCUS/LSIL cytology; No Response (NR) — persistent HR HPV positivity, with or without evidence of CIN1; Progression (PG) — persistent HR HPV positivity, with histopathologic evidence of progression to CIN2, 3,or invasive cancer.

The study also documented the toxicity of Polyphenon E compared to placebo in this cohort. The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 was used for adverse event description and grading.

2.4. Statistical analysis

The statistical analyses were performed for this trial used the intention-to-treat principle. The sample size estimate for this trial was based on a two-sided Fisher's exact test at a significance level of 0.05. The spontaneous regression rate for HPV at 4 months in the placebo group was estimated to be approximately 10% (based on our own work in the same study population) [10]. It was estimated that 68 participants per arm would allow for detection of a Polyphenon E related increase in the HPV clearance rate from 10% to 35%, with a power of 0.93. Based on these considerations and taking into account a potential loss to follow-up rate of 15%, we proposed enrolling 78 subjects in each arm.

Two-sample test with unequal variances was performed to compare each continuous baseline variable between groups. Fisher's exact test was performed to compare each categorical baseline variable between groups. Fisher's exact test was also performed to compare each of the primary outcomes, HR HPV clearance and histologic resolution, between groups. In addition, for each primary outcome, logistic regression was performed to adjust for participant's baseline characteristics, such as age, smoking status, current sexual activity, lifetime partners, age at first intercourse and race/ethnicity.

Finally, a scheduled interim futility analysis was conducted at the midpoint of enrollment for the trial which led to early closure of the trial. Pre-specified stopping rules were that the study would be discontinued if the complete regression rate in the treatment group was equal to or less than the rate observed in the placebo group. Based on the expected rates of 10% regression in placebo and 35% regression in the treatment group and interim sample sizes of 39 subjects per group, the probability of committing type II error (i.e., halting the trial when in fact the true placebo and treatment rates are as expected) was approximately 0.004. Thus, the interim analysis has a negligible effect on overall statistical power.

3. Results

The study was closed to accrual based on the results of the protocol-specified interim futility analysis. In total 208 women were screened for eligibility at the three study centers. The screen fail rate was higher than anticipated with HPV negativity, absence of CIN and high-grade CIN as the top three screen fail reasons. Ninety-eight women met all eligibility criteria and were randomized to one of two study arms. The Consort flow diagram is shown in Fig. 1.

Of 50 participants randomized to receive Polyphenon E, 35 completed the intervention, six discontinued intervention early with response outcome data, one discontinued intervention early without response outcome data, seven were lost to follow-up, and one withdrew consent. Of the 48 participants randomized to receive placebo, 38 completed the intervention, three discontinued but had evaluable response outcome data, five were lost to follow-up, one was non-compliant with study procedures, and one withdrew consent.

Subject characteristics for the entire study population are summarized in Table 1. The age range was balanced between the two treatment groups with the mean age of 28.48 in the Polyphenon E group and 28.27 in the placebo group. The treatment groups are also well balanced in terms of smoking status, sexual history and race/ethnicity. Of note, our trial included a high proportion of Hispanic participants (45% overall).

Table 2 summarizes the response outcome data by treatment group. In keeping with an intent-to-treat analysis, all participants with response outcome data ($n = 41$ in each arm) were included in the analysis. There was no difference in response rate by treatment allocation. Complete response, that is a negative HR HPV and normal histopathology, was noted in 7 (17.1%) and 6 (14.6%) for the treatment and placebo arms respectively. Partial response occurred more frequently in the placebo group and progression was more common in the treatment group, although neither of these findings were statistically significant. A logistic regression analysis which accounted for treatment group, age, smoking status, current sexual activity, lifetime partners, age at first intercourse and race/ethnicity failed to reveal any treatment effect when these variables were considered (data not shown). In addition, analyses to assess differences between treatment and placebo arms if grouped by ages under and over 30 years showed no significant differences (data not shown).

HPV outcome data by treatment group included all participants with HPV outcome data ($n = 41$ in each arm) in the analysis (Table 3). Likewise, end of study HR HPV positive status was found to be similar between the two groups with 31 (75.6%) in the Polyphenon E group and 29 (70.7%) in the placebo arm ($p = 0.80$), and was not modified by logistic regression analysis that accounted for co-variables (data not shown).

All participants with histological outcome data ($n = 41$ in the Polyphenon E arm; $n = 39$ in the placebo arm) were included in the analysis of histological outcomes by treatment group (Table 4). The histological outcomes were similar for the Polyphenon E and placebo groups. More than half of all subjects had normal histology at the conclusion of the trial regardless of treatment group allocation. There was a statistically non-significant histological progression to CIN2 in the Polyphenon E group with 7 cases (17.1%) compared to 3 cases (7.7%) in the placebo.

In general, the study agent was well tolerated by study participants. Medication adherence, as measured by pill count, was found to be excellent across the two groups, and was further substantiated by urinary catechin metabolite testing, with the average urinary EGC concentration measured at 652 ng/ml in the Polyphenon E arm compared to 59 ng/ml in the placebo arm. There were a total of 163 and 136 adverse events in the placebo and Polyphenon E groups, respectively. Two serious adverse events occurred in one participant in the placebo arm with both events attributed to changes in seizure and anxiety medications. Two participants in the Polyphenon E group discontinued the study early due to adverse events (one for gastrointestinal related events and the other for ALT and AST elevation). One participant in the placebo group discontinued intervention early due to adverse events (for persistent ALT and AST elevation).

Adverse events occurring in greater than 5% of subjects treated with Polyphenon E or placebo, regardless of attribution, were documented. These were all Grade 1 or Grade 2 events, except one Grade 3 ALT elevation and one Grade 3 back pain in the Polyphenon E arm and one Grade 3 ALT and AST elevation in the placebo arm. Nausea was reported more frequently by subjects receiving Polyphenon E compared to those receiving placebo, 32.0% vs. 18.8%, respectively. Other AEs that occurred more frequently in the Polyphenon E arm than that in the placebo arm include vomiting (6.0% vs. 2.1%), cervicitis (12.0% vs. 6.3%), sinus infection (6.0% vs. 0%), dizziness (14.0% vs. 6.3%), back pain (6.0% vs. 4.2%), stomach ache (12.0% vs. 8.3%), upper respiratory conditions related to cold symptoms (8.0% vs. 6.3%), and irregular menses (6.0% vs. 4.2%). In addition, elevated ALT was noted in 10.0% of subjects in the Polyphenon E group compared to 2.1% in the placebo group. Elevated AST was noted
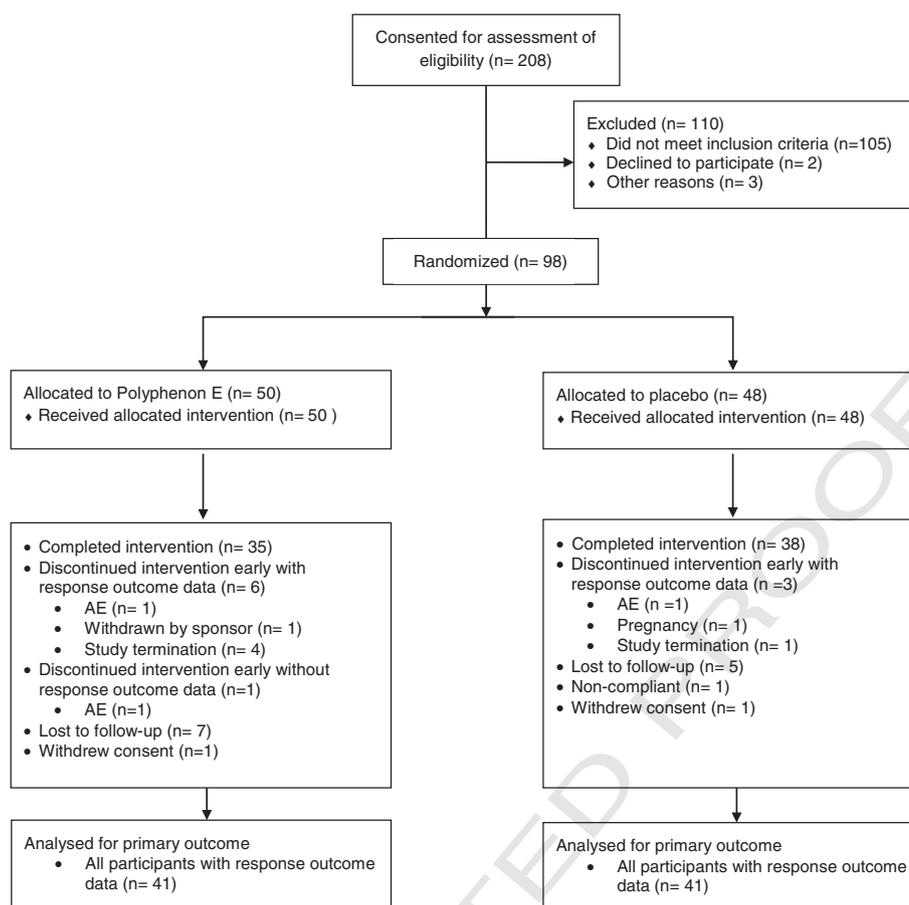
Fig. 1. Consort flow diagram.

314 in 8.0% of subjects in the Polyphenon E group compared to 2.1% in the
315 placebo group. It should be noted that in all cases the liver function
316 tests returned to baseline after discontinuation of study agent, although
317 in one case this did not occur until approximately 6 months post
318 discontinuation. A summary of adverse events is provided in Supple-
319 mentary Table 2.

4. Discussion

321   The search for chemopreventive agents for use in cervical cancer
322 prevention is logical given the well characterized, protracted
323 preinvasive character of CIN, encouraging preclinical laboratory data,
324 and epidemiologic findings that suggest a protective role for a variety
325 of nutritional agents. These chemoprevention studies, however, have
326 been largely disappointing and plagued by a variety of methodological
327 challenges. Problems include a lack of consensus as to the appropriate
328 grade of disease to be studied (CIN1, 2 or 3), the appropriate definition
329 of response (e.g. histologic regression, viral clearance) given significant
330 rates of spontaneous regression, the selection of appropriate endpoint
331 biomarkers, as well as ethical and safety considerations (withholding
332 treatment for potentially preinvasive disease).

333   Despite these challenges, a significant number of trials have been
334 conducted in this area over the past 30 years. Investigators have long
335 shown great interest in looking at the role of micronutrients and phar-
336 maceutical interventions in cervical cancer prevention. Although some
337 success has been found in animal models, most have shown mixed
338 results in human trials. In our review of 22 combined clinical trials
339 (Supplementary Table 1) that assessed a variety of interventions includ-
340 ing antioxidants, suicide inhibitors of ornithine decarboxylase, reti-
341 noids, and micronutrients. There was no consistent clinical effect for
342 any of these interventions. Chemoprevention trials conducted among

343 women with high-grade cervical intraepithelial neoplasia using reti-
344 noids [11], ß-carotene [12], difluoromethylornithine [13], indole-3-
345 carbinol [14], amilogene [15], and cyclooxygenase inhibitors have
346 been largely inconclusive and were associated with patient acceptabili-
347 ty concerns.

348   Green tea, green tea extract, green tea catechins, and EGCG have
349 been shown to inhibit carcinogenesis induced by a wide variety of
350 carcinogens in rodent cancer models. The principal components in
351 green tea are catechins (30–42%) and flavonols (5–10%). The major
352 catechins are $(-)$-epicatechin (EC), $(-)$-epicatechin gallate (ECG),
353 $(-)$-epigallocatechin (EGC), and $(-)$-epigallocatechin gallate
354 (EGCG), with EGCG being the most abundant. Tea is one of the most
355 widely consumed beverages worldwide, although utilization varies
356 greatly in different populations. Tea is manufactured in three basic
357 forms: black, green, or oolong, which differ mostly in the degree of
358 oxidation during production. Additionally, green tea's relative low cost
359 makes it an attractive agent for chemoprevention in low resource
360 settings.

361   In this study, we sought to investigate the effect of Polyphenon E in
362 women with persistent HR HPV infection and concomitant CIN1 to eval-
363 uate the potential of Polyphenon E for cervical cancer prevention. This
364 was based on promising pre-clinical data showing that green tea,
365 green tea extract, green tea catechins, and EGCG inhibit carcinogens;
366 and on preliminary clinical data showing regression of cervical dysplasia
367 with Polyphenon E. In addition, potential advantages for Polyphenon E
368 as a chemopreventive agent are a presumed high patient acceptability
369 and safety profile.

370   We have now conducted the largest randomized placebo-controlled
371 trial of a green tea extract for HPV related cervical disease. Definitive re-
372 sults show that Polyphenon E is acceptable, safe and well tolerated.
373 However, despite the promising *in vitro* data and the pilot clinical

Table 1

Characteristics of the study population.

Variable	All subjects (98)	Poly-E (50)	Placebo (48)	p-value[a]
Age				0.9020
Range	18–58	19–58	18–56	
Mean	28.38	28.48	28.27	
Standard deviation	8.39	8.78	8.05	
Weight(pounds)				0.9034
Range	89–307	89–268	92–307	
Mean	149.29	149.78	148.77	
Standard deviation	40.83	39.48	42.63	
Height (inches)				0.7077
Range	53–72	56–72	53–70	
Mean	63.69	63.58	63.81	
Standard deviation	3.01	2.85	3.20	
Race				0.6470
American Indian	2 (2%)	1 (2%)	1 (2%)	
Asian	3 (3%)	0	3 (6%)	
African American	5 (5%)	3 (6%)	2 (4%)	
White	78 (80%)	41 (82%)	37 (77%)	
Other (including mixed)	3 (3%)	1 (2%)	2 (4%)	
Unknown	7 (7%)	4 (8%)	3 (6%)	
Ethnicity				1.0000
Hispanic	44 (45%)	22 (44%)	22 (46%)	
Non-Hispanic	54 (55%)	28 (56%)	26 (54%)	
Smoking status				1.0000
Never smoked	79 (81%)	40 (80%)	39 (81%)	
Past smoker	5 (5%)	3 (6%)	2 (4%)	
Current smoker	14 (14%)	7 (14%)	7 (15%)	
Current sexual activity				0.6317
No	22 (22%)	10 (20%)	12 (25%)	
Yes, one partner	75 (77%)	39 (78%)	36 (75%)	
Yes, >one partner	1 (1%)	1 (2%)	0	
Age at first intercourse				0.8283
Range	12–23	14–23	12–23	
Mean	16.7	16.8	16.7	
Standard deviation	2.26	2.20	2.34	
Total lifetime partners				0.0890
Range	1–50	1–50	1–20	
Mean	7.5	8.7	6.3	
Standard deviation	7.01	8.61	4.71	

[a] Based on a two-sample t-test with unequal variances for continuous variables and a Fisher's exact test for categorical variables.

data, in our study, Polyphenon E was not shown to promote the resolution of persistent HR HPV and related CIN1. However, perhaps intervention at different points in the development of SIL/cancer may yield different results. Since primary HPV screening is done now over age 30 years, intervening early with HR HPV positive cases with no SIL, or HPV genotyping may show that HPV 16/18 have different response to these kinds of treatments than other HR HPV. In addition, intervening as an adjuvant to established treatment of HSIL may have improved outcomes and decreased progression. The development of other molecular markers of progression may also identify specific populations that would be responders or non-responders to these novel chemopreventive treatments.

There are several limitations and strengths to our study that should be noted. One limitation is the length of follow-up of 4 months for our study, which was selected due to concern about a small but real risk for disease progression. Even though all participants had documented persistent HPV infections, the duration of the persistence could potentially be incidental. However, this should have been accounted for by the randomization procedure to balance known and unknown factors between groups. Another potential limitation one could argue is that

Table 3

HPV outcomes by treatment group.

Group	Negative	Positive	Total
Poly-E	10 (24.4%)	31 (75.6%)	41
Placebo	12 (29.3%)	29 (70.7%)	41

The p-value is 0.80 based on a Fisher's exact test.

Table 4

Histological outcomes by treatment group allocation.

Group	Normal	CIN1	CIN2	Total
Poly-E	21 (51.2%)	13 (31.7%)	7 (17.1%)	41
Placebo	21 (53.9%)	16 (38.5%)	3 (7.7%)	39

p-value = 0.47 based on a Fisher's exact test.

the catechins may not distribute extensively to the target tissue. Use of a vaginal agent rather than an oral agent could have been more effective. A final potential limitation is that it could be argued that the 10% spontaneous regression rate was too low and would under-power the study. This threshold was selected based on the regression rate of high-grade disease in the setting of HR HPV infection. This was used as a best proxy for the regression rate of persistent HR HPV infection.

A strength of this study was that it was a randomized, double-blind placebo-controlled study, which is the gold standard to reduce spurious causality and bias. Other strengths of this study include the assessment of clinically meaningful histologic and viral endpoints, a high degree of adherence across patients, and verification of agent intake using urine catechin metabolites.

Trials conducted to date in cervical chemoprevention have been mostly disappointing. There remains a tremendous need to find acceptable, safe, and inexpensive non-surgical treatments to prevent cervical cancer. These clinical studies are methodologically difficult to conduct due to very high rates of spontaneous regression of high-risk HPV infection, even in the setting of persistence. In addition, there is significant variation in the performance and yield of colposcopy that is operator dependent and that impacts the determination of study endpoints. Finally, there is a lack of consensus as to a reference standard that would be less invasive than an LEEP/conization that would be acceptable in this population of young reproductive age women. Further studies will continue to be necessary in order to develop better methodologies to facilitate evaluation of chemopreventive strategies in this organ site.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2013.12.034.

Conflict of interest statement

Acknowledgements

Table 2

Summary of response outcomes by treatment group designation.

Group	Progression (P)	No Response (NR)	Partial Response (PR)	Complete Response (CR)	Total
Poly-E	6 (14.6%)	27 (65.9%)	1 (2.4%)	7 (17.1%)	41
Placebo	3 (7.7%)	26 (63.4%)	6 (14.6%)	6 (14.6%)	41

The p-value is 0.21 based on a Fisher's exact test.

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