Protective effects of green tea extracts (polyphenon E and EGCG) on human cervical lesions

W-S Ahn[1], J Yoo[2], S-W Huh[3], C-K Kim[4], J-M Lee[1], S-E Namkoong[1], S-M Bae[3] and I P Lee[3]

We investigated clinical efficacy of green tea extracts (polyphenon E; poly E and (−)-epigallocatechin-3-gallate [EGCG]) delivered in a form of ointment or capsule in patients with human papilloma virus (HPV) infected cervical lesions. Fifty-one patients with cervical lesions (chronic cervicitis, mild dysplasia, moderate dysplasia and severe dysplasia) were divided into four groups, as compared with 39 untreated patients as a control. Poly E ointment was applied locally to 27 patients twice a week. For oral delivery, a 200 mg of poly E or EGCG capsule was taken orally every day for eight to 12 weeks. In the study, 20 out of 27 patients (74%) under poly E ointment therapy showed a response. Six out of eight patients under poly E ointment plus poly E capsule therapy (75%) showed a response, and three out of six patients (50%) under poly E capsule therapy showed a response. Six out of 10 patients (60%) under EGCG capsule therapy showed a response. Overall, a 69% response rate (35/51) was noted for treatment with green tea extracts, as compared with a 10% response rate (4/39) in untreated controls ($P<0.05$). Thus, the data collected here demonstrated that green tea extracts in a form of ointment and capsule are effective for treating cervical lesions, suggesting that green tea extracts can be a potential therapy regimen for patients with HPV infected cervical lesions. *European Journal of Cancer Prevention* 12:383–390 © 2003 Lippincott Williams & Wilkins.

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[1]Department of Obstetrics and Gynaecology, [2]Department of Pathology, [3]Catholic Research Institutes of Medical Science, College of Medicine, The Catholic University of Korea, 505 Banpo-Dong, Seocho-Ku, Seoul 137–040, Korea and [4]College of Pharmacy, Seoul National University, Shinlim-Dong, Kwanak-Ku, Seoul, 151–742, Korea.

Correspondence to W S Ahn. Fax: (+82) 2 599 4120.
E-mail: ahnws@catholic.ac.kr

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Introduction

Green tea is one of the most widely consumed beverages. Its possible beneficial properties have received increased attention. Consumption of green tea has been reported to lower the risk of developing gastric, pancreatic and colorectal cancers in human populations (Yu *et al.*, 1995; Ji *et al.*, 1997). Furthermore, anti-proliferative effects of green tea preparations have been demonstrated in many cancer cell lines, including those involving liver, fore stomach, skin, lung and oesophagus (Chen, 1992; Graham, 1992; Yamane *et al.*, 1996; Khafif *et al.*, 1998). The anti-carcinogenic and anti-proliferative effects of tea have been attributed to the biological properties of green tea polyphenolic compounds. The polyphenols account for up to 30% of the dry weight of green tea and include flavanols, flavandiols, flavonoids and phenolic acids (Graham, 1992). In particular, flavanols, known as catechins, are a major component of most green tea. The catechins are composed of (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), (−)-epicatechin (EC), (+)-gallocatechin (GC) and (+)-catechin (C). Among these, EGCG, a major constituent of catechins, has been shown to be the most effective for inhibiting tumour cell growth as well as inducing apoptosis (Ahmad *et al.*, 1997; Asano *et al.*, 1997). EGCG has also demonstrated anti-carcinogenic activities in animal models including those for skin, lung, breast, prostate and gastrointestinal tract cancers (Katiyar *et al.*, 1992; Yang and Wang, 1993; Liao *et al.*, 1995). Inhibition of lung metastasis with mouse melanoma cells was also demonstrated by EGCG treatment in mice (Taniguchi *et al.*, 1992). *In vitro* studies have also shown that EGCG can inhibit the growth of human mammary and lung cancer cells (Komori *et al.*, 1993), prostate cancer cells (Paschka *et al.*, 1998), lymphoma cells (Ahmad *et al.*, 1997), leukaemic cells (Otsuka *et al.*, 1998), and lung and colon cancer cell lines (Yang *et al.*, 1998). Anti-tumour effects of EGCG have been reported to be mediated by apoptosis (Ahmad *et al.*, 1997; Kennedy *et al.*, 2001; Paschka *et al.*, 1998; Yang *et al.*, 1998), inactivation of transcription factors (Okabe *et al.*, 1999), inhibition of urokinase and mitogen-activated protein kinase activities (Jankun *et al.*, 1997), suppression of lipo-oxygenase and cyclo-oxygenase activities (Stoner and Mukhtar, 1995), and G_1 arrest of the cell cycle (Ahmad *et al.*, 1997, 2000, 2002). EGCG has also been reported to be incorporated into the phospholipid bilayer membrane, leading to blocking the tumour promoters from binding to their receptors within the cell membrane as a possible mechanism of EGCG for tumour growth inhibition

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(Okabe *et al.*, 1999; Otsuka *et al.*, 1998). Kennedy *et al.* (2001) recently reported that green tea extract causes cytochrome c release and caspase activation for induction of apoptosis. More recently, it has been reported that EGCG inhibits the activity of topoisomerase I, which plays a critical role in DNA replication, transcription, and chromosome condensation (Berger *et al.*, 2001). EGCG also inhibits tumour cell growth by suppressing vascular endothelial growth factor (VEGF) induction in human colon cancer cells (Jung *et al.*, 2001). Taken together, it is likely that EGCG inhibits cancer cell growth through many different regulatory pathways, along with apoptosis and cell cycle arrests.

Cervical cancer is an important cause of death in women worldwide. It is caused mostly by infection with human papillomavirus (HPV) (Ji *et al.*, 1997; Yu *et al.*, 1995). The oncogenic HPV proteins, E6 and E7 play a critical role in inducing cervical cancers by interacting with p53 and pRb for inactivation of these cellular regulatory proteins, respectively (Scheffner *et al.*, 1990; Werness *et al.*, 1990). Presently, the surgical and radiation therapies have been approached with limited success. Furthermore, an early detection of cervical cancer using the Pap smear has contributed to decreased incidence of cervical cancers. Despite the great progress in treating cervical cancers in the last three decades, recurrent or persistent cervical cancers have been problematic, adding the importance of developing anti-cervical cancer drugs. Local application of EGCG to the skin and cervical cancer lesions has been reported to suppress the lesion by directly blocking the progression to the next phases of carcinogenesis (Kang *et al.*, 2000; Cutter *et al.*, 2001; Annabi *et al.*, 2002). We also reported that EGCG possesses anti-tumour activities against a cervical cancer cell line (Ahn *et al.*, 2003), suggesting that green tea extracts could be a possible drug candidate for treating cervical cancer.

In this study, we investigated if green tea extracts in a different form (poly E ointment, poly E capsule and EGCG capsule) might confer chemopreventive efficacy to patients with cervical lesions. For clinical evaluations, morphological changes of cervical lesions and detection of HPV DNA were measured.

Methods and materials

Patients

Eighty-eight patients who visited the Kangnam St Mary Hospital, the Catholic University of Korea, from January 1998 to May 2001 were evaluated in this study under the patient's consent. The patients were randomised for this study. The Ethical Committee of the Kangnam St Mary Hospital approved this trial. Clinical disease status was determined by cytology, cervicography, colposcopy, histology and HPV DNA test.

Drugs, doses and delivery methods

Poly E ointment, poly E capsule and EGCG capsules were kind gifts from Dr Yukihiko Hara from the Mutsui Norin Company, Fujied, Japan. For local poly E treatment, poly E ointment was given locally to the cervical dysplasia lesions of patients twice a week. Clinical disease status was monitored at four-week intervals. For oral treatment with poly E or EGCG capsule, a dose of 200 mg per day of poly E or EGCG was given to patients for eight to 12 weeks. The pharmacokinetic study of this dose was previously reported (Sherry Chow *et al.*, 2001). For combination therapy, two protocols were applied at the same time to patients. As a control, patients were untreated and evaluated over the same time scales as the treatment groups.

Toxicity and side effects

Haematological and non-haematological toxicities as well as adverse side effects in patients treated locally or systemically with poly E and EGCG were evaluated at four-week intervals for 12 weeks.

Detection methods

Cytology, cytoscopy, colposcopy, histology, cervicography and HPV DNA test were used in this study. In particular, the DNA-RNA hybrid capture assay was performed for HPV DNA detection at four-week intervals for four to eight weeks.

Evaluation

In the case of HPV-infected patients, cases showing a decrease in or loss of HPV DNA titres were considered as a positive response. In cytology, no detection of abnormal cells or decrease in the lesion extent was considered a positive response. In tissue biopsy, patients showing no lesion were considered as a positive response.

Statistical analysis

McNemar or Chi-Square test was used for statistical analysis. The P values less than 0.05 were considered statistically significant.

Results

Pap smear observation after local application of poly E ointment and/or oral delivery with poly E or EGCG capsules

We evaluated the lesion extent by Pap smear cytology before and after treatment with poly E and/or EGCG in patients (Table 1). In the case of poly E ointment, three out of four patients with atypical squamous cells of undetermined significance (ASCUS) (75%), 10 out of 12 patients with low-grade squamous intraepithelial lesions (LSIL) (83%) and three out of four patients with high-grade squamous intraepithelial lesions (HSIL) (75%) showed positive responses after treatment. In contrast, an

Table 1 Changes in Papanicolaou cytology of cervical pre-cancerous lesions by treatment with poly E ointment and/or poly E or EGCG capsules. Patients were treated with poly E and/or EGCG for 8–12 weeks and Pap smear cytology was tested at four-week intervals for 4–12 weeks

Group	Lesion extent	Pre-treatment (# patients)	Post treatment (# patients)				
			WNL	RC	ASCUS	LSIL	HSIL
Poly E ointment	WNL	2	1	1	0	0	0
	RC	5	1	3	1	0	0
	ASCUS	4	2	1	0	1	0
	LSIL	12	4	6	0	1	1
	HSIL	4	0	3	0	0	1
Poly E ointment	WNL	0	0	0	0	0	0
Plus	RC	1	0	1	0	0	0
Poly E capsules	ASCUS	1	0	1	0	0	0
	LSIL	4	1	2	0	0	1
	HSIL	2	0	2	0	0	0
Poly E capsules	WNL	2	0	2	0	0	0
	RC	0	0	0	0	0	0
	ASCUS	1	0	1	0	0	0
	LSIL	1	1	0	0	0	0
	HSIL	2	0	1	0	0	1
EGCG capsules	WNL	0	0	0	0	0	0
	RC	1	0	0	1	0	0
	ASCUS	1	0	0	0	0	1
	LSIL	0	0	0	0	0	0
	HSIL	8	3	2	0	1	2
CCNH	WNL	10	5	5	0	0	0
	RC	16	5	8	0	0	3
	ASCUS	3	2	1	0	0	0
	LSIL	6	1	3	0	1	1
	HSIL	4	0	1	1	0	2

WNL, within the normal limit. RC, reactive cellular change. ASCUS, atypical squamous cells of undetermined significance. LSIL, low-grade squamous intraepithelial lesions. HSIL, high-grade squamous intraepithelial lesions.

insignificant number of the remaining patients showed no change or had became worse.

In the case of treatment with poly E ointment plus poly E capsules, one ASCUS and two HSIL patients showed a positive response. Three out of four LSIL patients displayed positive responses except for one patient who became worse. In the case of poly E capsule treatments, two patients within the normal limit (WNL), one patient with ASCUS and one patient with LSIL showed a positive response. One out of two patients with HSIL showed a positive response while one remaining patient became worse.

In the case of oral delivery with EGCG capsules, one patient with reactive cellular change (RC) exhibited further aggravation to the lesion extent. In contrast, five out of eight patients with HSIL showed a complete recovery while the remaining three patients were either the same as before or had less severe lesion extent than before treatment started. One patient with ASCUS became worse.

In the untreated control groups, however, three out of 16 patients with reactive cellular change (RC) became HSIL; three patients with ASCUS became either WNL (within normal limit) or RC; four out of six patients with LSIL became either WNL or RC and the remaining patients were either the same as before or had more severe lesions than before. Two of four HSIL patients became either RC or ASCUS while the remaining two patients remained in the same HSIL stage.

HPV DNA test after local application of poly E ointment and/or oral delivery with poly E or EGCG capsules

We evaluated the presence of HPV DNA in the lesion by hybrid capture assay before and after treatment with poly E and/or EGCG (Table 2). In the case of poly E ointment, 13 out of 18 chronic cervicitis (CC) patients, three out of five cervical intraepithelial neoplasia (CIN I, mild dysplasia) patients, both the two patients with moderate dysplasia (CIN II) and both the two patients with severe dysplasia (CIN III) were positive for HPV DNA prior to treatment. After treatment, eight out of the 13 CC (62%), two out of the three CIN I (67%), both of the CIN II (100%) and one of the CIN III (50%) patients were negative for HPV DNA. In contrast, two out of the five CC patients who were negative for HPV DNA became positive for HPV DNA.

Table 2 Changes in HPV DNA of cervical pre-cancerous lesions by treatment with poly E ointment and/or poly E or EGCG capsules. Patients were treated with poly E and/or EGCG for 8–12 weeks and then HPV DNA was tested at four-week intervals for 4–12 weeks

Group	Dysplasia	Pre-treatment (# patients)		Post treatment (4–12 weeks) (# patients)							
	Degree	(+)	(−)	Disappear		Decrease		No change		Aggravated	
Poly E ointment	Chronic cervicitis	13	5	8	0	5	0	0	3	0	2
	Mild dysplasia	3	2	2	0	0	0	0	2	1	0
	Moderate dysplasia	2	0	2	0	0	0	0	0	0	0
	Severe dysplasia	2	0	1	0	0	0	0	0	1	0
Poly E ointment Plus Poly E Capsule	Chronic cervicitis	1	0	1	0	0	0	0	0	0	0
	Mild dysplasia	1	0	1	0	0	0	0	0	0	0
	Moderate dysplasia	2	0	1	0	1	0	0	0	0	0
	Severe dysplasia	3	1	2	0	1	0	0	1	0	0
Poly E capsule	Chronic cervicitis	2	0	2	0	0	0	0	0	0	0
	Mild dysplasia	1	1	0	0	1	0	0	1	0	0
	Moderate dysplasia	1	0	0	0	1	0	0	0	0	0
	Severe dysplasia	1	0	1	0	0	0	0	0	0	0
EGCG capsule	Chronic cervicitis	0	1	0	0	0	0	0	0	0	1
	Mild dysplasia	1	0	0	0	1	0	0	0	0	0
	Moderate dysplasia	1	0	0	0	0	0	0	0	1	0
	Severe dysplasia	7	0	5	0	1	0	0	0	1	0
CCNH	Chronic cervicitis	28	1	13	0	8	0	1	1	6	0
	Mild dysplasia	3	0	2	0	0	0	0	0	1	0
	Moderate dysplasia	2	0	2	0	0	0	0	0	0	0
	Severe dysplasia	5	0	0	0	3	0	1	0	1	0

In the case of local application with poly E ointment plus oral delivery with poly E capsules, all of CC, CIN I, CIN II and three out of four CIN III patients were positive for HPV DNA before treatment. However, one CC (100%), one CIN I (100%), one CIN II (50%), and two CIN III (67%) patients became negative for HPV DNA following treatment.

In the case of oral delivery with poly E capsules, both the CC patients, one of the two CIN I patients, and both of the CIN II and CIN III patients were positive for HPV DNA prior to treatment. The two CC patients (100%) and the CIN III (100%) patient became negative for HPV DNA following therapy. However, the CIN I, and CIN II patients were still positive for HPV DNA with the DNA titre a little decreased.

In the case of oral delivery with EGCG capsules, neither the CC patient, the CIN I, CIN II patient or all seven of the CIN III patients were positive for HPV DNA prior to treatment. However, five of the seven CIN III patients (71%) became negative for HPV DNA following treatment. In particular, one CC patient who was negative for HPV DNA prior to treatment became positive for HPV DNA after therapy. In the untreated control groups, 28 out of 29 CC, all of the three CIN I, both the CIN II and all five of the CIN III patients were positive for HPV DNA at week 0. Thirteen out of the 28 CC (46%), two of the three CIN I (67%), both of the CIN II (100%) and none of the five CIN III (0%) patients became negative for HPV DNA in weeks 4–12.

Tissue biopsy observation after local application of poly E ointment and/or oral delivery with poly E or EGCG capsules

We evaluated the dysplasia degree by tissue biopsy before and after treatment with poly E and/or EGCG in patients (Table 3). In the case of poly E ointment, 17 out of 18 CC (94%), four out of five CIN I (80%), both of the CIN II (100%) and one out of two CIN III (50%) patients showed a morphological change in the lesions without any histological alteration after treatment. However, one of the 18 CC patients became CIN III. Furthermore, one of the five CIN I patients became CIN II.

In the case of local application of poly E ointment plus oral delivery with poly E capsules, the sole CC patient (100%), one of the two CIN II (50%) and three of the four CIN III (75%) patients showed a complete loss of lesions following treatment, In contrast, one CIN I patient showed no change in the lesions. One remaining case with CIN II progressed to CIN III.

In the case of oral delivery with the poly E capsules, both of the CC (100%) and one of the two CIN I (50%) patients showed a complete loss of the lesions after treatment. However, one CIN II patient progressed to CIN III while one CIN III patient showed the same stage as before treatment.

In the case of oral delivery with EGCG capsules, cervical lesions disappeared in neither the CC, CIN I, CIN II or four of the seven (57%) CIN III patients following

Table 3 Changes in dysplasia degree of cervical pre-cancerous lesions by treatment with poly E ointment and/or poly E or EGCG capsules. Patients were treated with poly E and/or EGCG for 8–12 weeks and then tissue biopsy was tested at four-week intervals for 4–12 weeks

Group	Dysplasia degree	Pre-treatment (# patients)	Post treatment (4–12 weeks) (# patients)			
			Chronic cervicitis	Mild dysplasia	Moderate dysplasia	Severe dysplasia
Poly E ointment	Chronic cervicitis	18	17	0	0	1
	Mild dysplasia	5	4	0	1	0
	Moderate dysplasia	2	2	0	0	0
	Severe dysplasia	2	1	0	0	1
Poly E ointment	Chronic cervicitis	1	1	0	0	0
Plus	Mild dysplasia	1	0	1	0	0
Poly E capsule	Moderate dysplasia	2	1	0	0	1
	Severe dysplasia	4	3	0	1	0
Poly E capsule	Chronic cervicitis	2	2	0	0	0
	Mild dysplasia	2	1	1	0	0
	Moderate dysplasia	1	0	0	0	1
	Severe dysplasia	1	0	0	0	1
EGCG capsule	Chronic cervicitis	1	0	0	0	1
	Mild dysplasia	1	0	0	0	1
	Moderate dysplasia	1	1	0	0	0
	Severe dysplasia	7	4	1	0	2
CCNH	Chronic cervicitis	29	26	0	1	2
	Mild dysplasia	3	3	0	0	0
	Moderate dysplasia	2	2	0	0	0
	Severe dysplasia	5	2	0	0	3

treatment. However, both the CC and CIN I patients progressed to CIN III.

In the untreated control groups, 26 out of 29 CC (90%), all three of the CIN I (100%), both of the CIN II (100%) and two out of the five CIN III (40%) patients showed any loss of lesions. In particular, one and two of the 29 CC patients became CIN II and CIN III, respectively.

Toxicity and side effects

We evaluated whether systemic therapy with poly E and EGCG capsules might result in any toxicities in patients (Table 4). Haematological and non-haematological toxicities (leukopenia, neutropenia, anaemia, thrombocytopenia, emesis, diarrhoea, alopecia, myalgia, peripheral neuropathy) were not observed in any of the patients except for one patient who exhibited abnormal liver function after four weeks following poly E capsule treatment. However this patient became normal when tested at weeks 8 and 12 following the poly E capsule treatment.

We further evaluated any local side effects by applying poly E and EGCG ointments to the lesions (Table 5). Cervical inflammation, cervical vascularity, vaginal inflammation and other adverse events (burning, itching, irritation, discharge in vagina and vulva) were observed insignificantly over time after local therapy with the ointments. Thus, this suggests that poly E and EGCG are safe for clinical approaches.

Table 4 Haematological and non-haematological toxicity in patients following treatment with poly E or EGCG capsules. Patients were treated with poly E and/or EGCG for 8–12 weeks and then their toxicity was tested at four-week intervals for 12 weeks

Treatments	Poly E capsules*				EGCG capsules#			
Events weeks	0	4	8	12	0	4	8	12
Leukopenia	0	0	0	0	0	0	0	0
Neutropenia	0	0	0	0	0	0	0	0
Anaemia	0	0	0	0	0	0	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0
Emesis	0	0	0	0	0	0	0	0
Diarrhoea	0	0	0	0	0	0	0	0
Alopecia	0	0	0	0	0	0	0	0
Myalgia	0	0	0	0	0	0	0	0
Peripheral neuropathy	0	0	0	0	0	0	0	0
LFT (liver function test) abnormality	0	1	0	0	0	0	0	0

*The number of patients showing toxicity among six patients treated locally with Poly E ointment.
#The number of patients showing toxicity among 10 patients treated locally with Poly E ointment and with Poly E capsules.

Overall responses

As shown in Table 6, 20 out of 27 patients showed a response to local treatment with poly E ointment. Similarly, six out of eight patients undergoing combination therapy by local application of poly E ointment and oral delivery with poly E capsules showed a response. Three out of six patients recovered following treatment by oral delivery with poly E capsule. Six out of 10 patients undergoing oral delivery with EGCG capsules showed a positive response. Overall, 35 out of 51 patients under therapy with green tea extracts showed a positive response. This is in contrast to the untreated control

Table 5 Adverse local events following Poly E ointment therapy and Poly E ointment plus Poly E capsule therapy for 12 weeks. Patients were treated with poly E and/or EGCG for 8–12 weeks and then their adverse events were observed at four-week intervals for 12 weeks

Treatments	Poly E ointment*				Poly E ointment + Poly E capsule#			
Event weeks	0	4	8	12	0	4	8	12
Cervical								
Inflammation	1	0	0	0	0	1	0	0
Vascularity	0	0	0	0	0	0	0	0
Vaginal inflammation	0	1	0	0	1	0	0	0
Vaginal								
Burning	0	0	0	0	0	0	0	0
Itching	0	0	0	0	0	0	0	0
Irritation	2	0	0	0	1	0	0	0
Discharge	0	0	0	0	0	0	0	0
Vulva								
Burning	1	0	0	0	1	0	0	0
Itching	0	0	0	0	0	0	0	0
Irritation	0	0	0	0	0	0	0	0

*The number of patients showing toxicity among 27 patients treated locally with Poly E ointment.
#The number of patients showing toxicity among eight patients treated locally with Poly E ointment and Poly E capsules.

group in which only four of the 39 patients showed a positive response. However, little difference was observed between the groups undergoing single or combination therapy with poly E ointment, poly E capsule and EGCG capsules.

Discussion

A component of green tea, catechin has been known to possess anti-cancer properties. It suppresses the growth of cancer cells of various human origin including HPV-infected cervical cancer cell lines (Follen *et al.*, 2001; Gao *et al.*, 2002; Proniuk *et al.*, 2002; Sang *et al.*, 2002). In cervical cancers, chemopreventive drugs should be effective against pre-invasive neoplasia, dysplasia and intra-epithelial neoplasia without any toxic side effects. Drug therapy against cervical dysplasia is considered of significance for blocking further progression to a more severe stage of cervical neoplasia. From the epidemiological point of view, the development of invasive cervical cancer from cervical intraepithelial neoplasm takes at least 10–15 years, during which administration of EGCG or high consumption of green tea could either reduce the incidence of cervical cancer or delay the progression of pre-cancer lesions to cervical cancer. It has been reported that the concentration of EGCG in the blood after drinking 1.2 g of green tea reaches a maximum of 0.6 μM in humans (Lee *et al.*, 1995; Unno *et al.*, 1996). However, the average dose of EGCG required for inhibiting tumorigenesis is in the range of 0.2–0.3 μM in animals (Yang and Wang, 1993). Yamane *et al.* (1996) reported that a high dose of green tea consumption didn't show any harmful side effects in humans, suggesting that optimal effect can be achieved by increasing the dosage of EGCG. This is further supported by studies of Japanese groups showing that green tea is a cancer preventive agent that is effective both before cancer onset and after cancer treatment in breast cancer populations (Nakachi *et al.*, 1998; Suganuma *et al.*, 1999). In one report, retinyl acetate gel is effective for suppressing the progression of pre-cancerous lesions to cervical cancer with no toxicity (Romney *et al.*, 1985). In other clinical studies, retinamide II shows positive effects on removal of cervical lesions by 68.7% while all-trans-retinoic acid and indole-3-carbinol in the form of a cervical cap have also been demonstrated to be effective (Meyskens and Surwit, 1985; Meyskens *et al.*, 1994; Bell *et al.*, 2000).

In our observation, 13 out of 18 patients with chronic cervicitis showed a positive response when poly E ointment was applied. In contrast, only three of the 29 untreated patients showed a positive response. This suggests that use of poly E ointment is a potent chemopreventive approach for suppressing cervical carcinogenesis. This response rate is in line with that

Table 6 Overall response rates of the treatment of green tea extracts versus natural histology of HPV infected lesion as a control

	Chronic cervicitis		Mild dysplasia		Moderate dysplasia		Severe dysplasia		Total	
	Response	Non-response	Response	Non-response	Response	Non-response	Response	Non-response	Response	Non-response
Poly E ointment	13/18 (72%)	5/18 (28%)	4/5 (80%)	1/5 (20%)	2/2 (100%)	0/2 (0%)	1/2 (50%)	1/2 (50%)	20/27 (74%)	7/27 (26%)
Poly E ointment plus Poly E capsule	1/1 (100%)	0/1 (0%)	1/1 (100%)	0/1 (0%)	1/2 (50%)	1/2 (50%)	3/4 (75%)	1/4 (25%)	6/8 (75%)	2/8 (25%)
Poly E capsule	2/2 (100%)	0/2 (0%)	1/2 (50%)	1/2 (50%)	0/1 (0%)	1/1 (100%)	0/1 (0%)	1/1 (100%)	3/6 (50%)	3/6 (50%)
EGCG capsule	0/1 (0%)	1/1 (100%)	0/1 (0%)	1/1 (100%)	1/1 (100%)	0/1 (0%)	5/7 (71%)	2/7 (29%)	6/10 (60%)	4/10 (40%)
Total	16/22 (73%)	6/22 (27%)	6/9 (67%)	3/9 (33%)	4/6 (67%)	2/6 (33%)	9/14 (64%)	5/14 (36%)	35/51 (69%)	16/51 (31%)
CCNH	3/29 (10%)	26/29 (90%)	0/3 (0%)	3/3 (100%)	1/2 (50%)	1/2 (50%)	0/5 (0%)	5/5 (100%)	4/39 (10%)	35/39 (90%)

of CIN I, CIN II and CIN III patients. Overall, 20 out of 27 patients treated with poly E ointment, six out of eight patients treated with poly E ointment and poly E capsules in combination, three out of six patients receiving poly E capsules orally and six of 10 patients receiving EGCG capsules orally showed a positive response. This is in contrast to the untreated control groups in which only four of the 39 patients showed a positive response. This suggests anti-cancer effects are exerted by green tea extracts, EGCG and poly E. Furthermore, the efficacy appears to be similar between poly E and EGCG treated groups. In this case, however, about 10% of the response rate in the untreated group may be due to differences in the immune status of the patients or other unknown factors.

In the process of local application with poly E, little inflammatory responses and abnormalities were observed in the cervical area. Furthermore, no systemic toxicity in the haematological and non-haematological events was observed during the oral treatment with poly E and EGCG capsules. In particular, one patient with thyroid malfunction showed increased serum glutamate oxaloacetate transaminase (aspartate aminotransferase; SGOT) and serum glutamate pyruvate transaminase (alanine aminotransferase; SGPT) levels, as determined by the liver function test. It is likely that green tea extracts and EGCG have no harmful effects in humans. Although the population size of this study was small, this clinical observation, however, clearly demonstrated that poly E/EGCG ointment and capsules are an effective regimen for treating cervical dysplasia. This further warrants a larger scale clinical trial where poly E/EGCG ointment and capsules are used for suppressing subsequent progression of cervical dysplasia to the next grade of cervical carcinogenesis.

In summary, these collective studies suggest that green tea extracts (poly E and EGCG) with anti-cancer properties might be an effective chemopreventive option for preventing cervical dysplasia from progressing to a more severe stage of cervical neoplasia.

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