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World J Gastroenterol 2002;8(3):418-422
World Journal of Gastroenterology
 ISSN 1007-9327

• ESOPHAGEAL CANCER •

Field Population-based blocking treatment of esophageal epithelia dysplasia

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Received 2001-12-20 **Accepted** 2002-02-07

Abstract

AIM: **To confirm the value of blocking treatment by zenshengping (ZSP), a Chinese herb composite, and Riboflavin for esophageal epithelia dysplasia cases screened out in high risk area in northern china by exfoliative balloon cytology (EBC), so to reduce the incidence rate of esophageal cancer(EC).**

METHODS: **Esophageal epithelium dysplasia cases including mind esophageal epithelium dysplasia (MEED), stage one severe esophageal epithelium dysplasia (SEEDI), and stage two severe esophageal epithelium dysplasia (SEEDII) were screened out from people aged 40 years and older in the high risk area of Chixian. These cases were randomly divided into a treatment and control group. Subjects in the treatment and control groups took ZSP, riboflavin, and placebo daily for three years. EC cases registered by cancer registry and identified by EBC re-screening in the treatment and control groups were used to calculate incidence and blocking rates to demonstrate the effects of blocking medication.**

RESULTS: **It was found that 31.92% and 24.15% of people aged 40 years and older in Cixian could been diagnosed as MEED and SEED cases. The severity of dysplasia increased with age. ZSP had blocked EC occurrence by 47.79% after 3 year medication among the SEED cases.**

CONCLUSION: **ZSP can block the development from SEEDIand SEEDII to EC by 47.79%. Efforts should be made to screen and treat dysplasia cases in people aged 40 years and older in high risk areas to reduce the mortality figures.**

Hou J, Lin PZ, Chen ZF, Ding ZW, Li SS, Men FS, Guo LP, He YT, Qiao CY, Guo CL, Duan JP, Wen DG. Field Population-based blocking treatment of esophageal epithelia dysplasia. *World J Gastroenterol* 2002;8(3):418-422

INTRODUCTION

The prognosis of esophageal and cardia cancer is the worst among digestive carcinomas because more than 90% of all its patients are clinically detected at advanced stages, and most of the patients can undergo only non-curative surgery due to either local tumor invasion into the surrounding tissue or distant metastasis at the time of operation[1-3]. The five year survival rate for clinically diagnosed EC is below 10%. On the other hand, treatment results for early digestive carcinomas are excellent. Several strategies exist for early treatment, including surgery, endoscopic resection, Chinese herbs, etc. The five year survival of early treated EC and gastric cancer patients can reach 90% or more[4-16]. Because most EC and gastric patients have no apparent symptoms until the disease develops into advanced stages, early diagnosis at hospitals seems unrealistic presently, and early detection is undergone mostly among high risk populations in area with high incidence by means of exfoliative ballon cytology (EBC) and/or endoscopy[17-24].

Besides treatment of early ECs such as carcinoma in situ or intramucosal carcinoma, another promising strategy of secondary prevention is receiving great interest presently. A number of researchers have demonstrated that esophageal epithelium dysplasia (EED) is a precancerous lesion which can either develop further into a more severe stage or cancer, stay unchanged, or reverse back to normal again for a period of several years or even a decade. It is therefore very promising to detect patients with EED and treat the precancerous lesions before they transform into the irreversible malignant stage in high risk populations[25-31]. There are several techniques and chemicals or nutrients that have been reported to be effective in blocking precancerous lesions from transforming into cancer[32-42]. Linpeizhong reported that an herb composite named Zenshengpin (ZSP) had shown an inhibitory rate of 50% after three years of medication for SEEDI and SEEDIIcases[25]. The present report came from "A Comprehensive Field Prevention and Treatment Study of Esophageal Cancer" carried out in the Chixian county of Hebei Province, which is adjacent to the Linxian county of Henan province, and also has the highest incidence rate of ECs in the world. This study was one of The National Eighth-Five-Year Scientific Championship Project. Its aim was to explore the feasibility of massive screening for EED patients among high risk people and to examine the long term effects of blocking treatment by ZSP and micronutrients in large samples of EED cases.

MATERIALS AND METHODS

Chixian is situated at 36°30" northern latitude, 114°40" eastern longitude, on the east side of the Taihang Mountain, along the Zhanghe River. Across the river to the south is the Anyang City of Henan province. Chixian county occupies an area about 951 square kilometers, and its population is 583611. There is a remarkable variation in the earth stratum of the county, with moutainous, hilly, and level land each constituting about one-third of its total area. The climate is influenced mainly by the warm mainland seasonal wind. The average temperature is 18-25℃ and the waterfall is 600-700 millimeters. The major soil there is brown and light colored weed earth. Farm products include wheat, corn, millet, rice, red potato, and beans. Iron ane coal are the main minerals, and coal is the main local fuel of the county.

The National Eighth-Five-Year Scientific Championship Project chose people aged 40 years and older in nine rural administrative units in the hilly part of Chixian County as the study population. The hilly

part of the county has a higher incidence rate of EC than the plain part. The nine rural administrative units were further randomly divided into two districts; a treatment and a control district. The number of the study population was 122497. They resided in 101 villages. There was no significant difference in the sex and age distribution of the study population between the treatment and control districts. In preparation for a massive EBC screen of the study population to detect EC, near esophageal cancer (NEC), MEED, SEEDI, and SEEDII cases, a county wide conference was convened by the Chixian County government for local leaders and cancer prevention professionals from the three administrative levels including the county, the rural administration unit, and the villages. At the conference, special committees were set up on each of the three administration level to be responsible for the execution of the EBC massive screen in the areas under their authority. After the conference, a forceful propaganda campaign was carried out countywide to advertise the benefits of massive EBC screenings such as early detection, early treatment and satisfactory survival results. One day prior to the screening, personal contacts with potential examinees were made by local physicians to arrange details for the screening. At the beginning of the screening, physical examination was performed by physicians to exclude persons with serious contraindication to EBC examination, then EBC examination was performed by specialists. Four slides were prepared from specimens obtained by the procedure. The slides were afterwards examined by cytologists with no knowledge about the design of the study. Diagnosis was made according to the five grade cytology classification system including gradeInormal, grade II MEED, grade IIIa SEEDI, grade IIIb SEEDII, grade IV NEC, and grade V EC[28]. A diagnosis of cancer was made only after verification by at least three cytologists. Patients initially diagnosed with grade IIIa, grade IIIb, grade IV, and grade V were reexamined by electronic endoscopy with biopsy.

Finally, 16748 people of the study population in the two districts accepted EBC screening. MEED, SEEDI, and SEEDII patients screened out from the treatment district were pre-chosen as the treatment group; while those of the MEED, SEEDI and SEEDII cases detected from the control district were chosen to be the control group. There were 1566 cases of MEED and 1396 cases of SEED (including SEEDI and SEEDII) in the treatment group; and 3780 MEED and 2649 SEED cases in the control group. The MEED patients in the treatment group took 8 calcium tablets (CT) which were equivalent to 3 grams of caco3and 5 milligrams of riboflavin. The SEED patients in the treatment group took 8 ZSP tablets daily. The MEED and SEED cases in the control group took 8 placebo tablets which were the same in color and size as ZSP and CT. The medication of ZSP, CT and placebo continued for three years. Half a year after initiation of the medication, EC cases diagnosed in the treatment and control groups were registered by a cancer registry constructed specifically for the study. At the end of the three year medication, EBC screening was re-initiated to identify EC cases in the treatment and control groups. EC cases registered by the registry and identified by the EBC re-screening were summarized to calculate the incidence rates for the treatment and control groups respectively.

RESULTS

Detection rates of MEED, SEEDI, SEEDII, NEC, and EC

As in Table 1, there were 179 cases of EC, 172 of NEC, 866 of SEEDII, 3179 of SEEDI, and 5346 of MEED as detected by the initial EBC screening from the 16,748 high risk participants aged 40 years and older in the treatment and control districts. The detection rates of MEED, SEEDI,SEEDII, NEC, and EC were 31.92%, 18. 98%, 5.17%, 1.03%, and 1.07% respectively. As the age increased by 5 year intervals, the detection rates of MEED, SEEDI,SEEDII, NEC, and EC all increased from the lowest for the 40-year-old group to the highest for the 60-year-old group, but the amount of increase in the detection rates with increase of age was not equal for MEED, SEEDI,SEEDII, NEC, and EC. The increase was the sharpest for EC and the lowest for MEED. An odds ratio (OR) defined as the ratio of the detection rates of the 60-year-old group against that of the 40-year-old group was 5.78 for EC, 2.56 for NEC, 1.80 for SEEDII, 1.61 for SEEDI, and only 1.18 for MEED.

Table 1 Age distribution of detection rates of MEED, SEEDI,SEEDII, NEC, and EC by EBC screening

Histology Grade	Age										Total		OR
	40-		45-		50-		55-		60-				
	n	Rate%	*n*	Rate%	*n*	Rate%	*n*	Rate%	*n*	Rate%	*n*	Rate%	
Normal	2703	50.50	1578	43.83	1094	39.10	945	35.59	746	30.09	7021	41.92	0.60
MEED	1574	29.40	1100	31.76	928	33.17	882	33.22	862	34.77	5346	31.92	1.18
SEEDI	820	15.32	626	18.08	550	19.66	572	21.54	611	24.65	3179	19.98	1.61
SEEDII	208	3.89	151	4.36	166	5.93	167	6.29	174	7.02	866	5.17	1.80
NEC	28	0.52	39	1.13	29	1.04	43	1.62	33	1.33	172	1.03	2.56
EC	20	0.37	29	0.84	31	1.11	46	1.73	53	2.14	179	1.07	5.78
Total	5353		3463		2789		2655		2479		16748		

EBC re-screening

EBC re-screening was carried out at the end of the three year medication period to detect EC patients among the MEED, SEEDI, and SEEDII cases in the treatment and control groups. Among the 4045 SEED cases, 77 EC cases had been diagnosed and registered before EBC re-screening (Table 2). With them excluded, there were 3968 SEED cases who should have been re-screened, and in the end 2976 (75.00%) were re-examined. The re-screening completion rate for the treatment and control groups of SEED was 78.4% and 74.2% respectively. As for the 5346 MEED cases, with the 76 EC cases already diagnosed and registered prior to re-screening excluded, 3775 (71.63%) were re-screened. The re-screening rates for the MEED treatment and control groups were 75.6% and 74% respectively.

Registered EC cases and incidence rates

From half a year after initiation of ZSP and CT medication to the time of re-screening, 77 cases of EC were diagnosed and registered among the 4045 SEED cases (Table 2). The three-year incidence rate by registered EC cases alone for all of the SEED cases was 1.90% (77/4045), and for SEED in the treatment and control groups were 0.78% (11/1396) and 2.49% (66/2649) respectively. A significant difference existed between the incidence rates of the two groups (χ^2=14.21,P<0.01). For the 5346 MEED cases, 76 EC patients were registered. The three year incidence rate for all of the MEED cases was 1.42% (76/5346), and was 1.14% (18/1566) and 1.54% (58/3780) for MEED in the treatment and control groups respectively.

There was no significant difference between the incidence rates of the two groups (χ^2=1.17,P>0.05).

Table 2 Effect of blocking treatment of MEED and SEED cases by ZSP,CT, and PLACEBO after three year medication

MEED

Group	No. subjects	EC Diagnosed			Incidence Rates (%)	Block Rates (%)
		EBC Re-screening	Registration	Total		
Treatment	1566	10	18	28	1.79	
Control	3780	26	58	84	2.22	
Total	5346	36	76	112	2.10	19.37

SEED

Group	No. subjects	EC Diagnosed			Incidence Rates (%)	Block Rates (%)
		EBC Re-screening	Registration	Total		
Treatment	1396	17	11	28	2.01	
Control	3649	36	66	102	3.85	
Total	4045	53	77	130	3.21	47.79

Re-screened EC cases and prevalence rates

By EBC re-screening, 53 EC cases were detected from the 2976 SEED cases. The prevalence rate was 1.78% (53/2976) for all of the SEED cases combined, and was 1.61% (17/1054) and 1.87% (36/1922) for SEED cases in the treatment and control groups respectively. There was no significant difference between the prevalence rates of the two groups (χ^2=0.26, P>0.05). Among the 3775 MEED cases, 36 EC cases were diagnosed by EBC re-screening, with a prevalence rate of 0.95% (36/3775) for the MEED combined, 0.89% (10/1114) for the treatment group, and 0.97% (26/2661) for the control group. There was no significant difference in the prevalence rates between the two groups (χ^2=0.15, P>0.05).

Combined incidence and blocking rates

During the first three year follow-up, 242 diagnoses of EC were made by registration and re-screening from the 9,391 SEED and MEED cases, yielding a total incidence rate of 2.58% (242/9391) for SEED and MEED combined, 1.89% (56/2962) for the treatment group, and 2.89% (186/6429) for the control group. A significant difference existed between the two groups (χ^2=8.12, P<0.01). A blocking rate of 34.60% calculated as (2.89-1.89%)/2.89%×100% was obtained to assess the effects of a three year period of medication by ZSP and CT.

As in Table 2, 112 EC cases were accumulated by three year registration and EBC-re-screening from the 5346 MEED cases (76 registered and 36 screened out). An incidence rate of 2.10% (112/5346) was calculated for the whole MEED group, 1.79% (28/1566) for MEED in the treatment group, and 2.22% (84/3780) for MEED in the control group. The difference between the incidence rates of the two groups did not reach a significant level (χ^2=1.02, P>0.05), and a blocking rate of 19.37% was calculated to demonstrate the effect of CT for MEED cases.

130 EC cases were diagnosed from the 4045 SEED cases by three year registration and EBC re-screening (77 registered and 53 re-screened out). The incidence rate was 3.21% for all of the SEED cases, 2.01% (28/1396) for SEED in the treatment, and 3.85% (102/2649) for SEED in the control group. The difference between the incidence rates of the two groups reached a significant level (χ^2=10.00, P<0.01), and the blocking rate by ZSP for SEED was 47.79%.

Incidence and blocking rates of EC for SEEDI and SEEDII

As in Table 3, 69 EC diagnoses were made during the three year study period among the 3179 SEEDI cases. The incidence rate was 2.17% (69/3179) for all of the SEEDI cases, 1.66% (20/1206) for SEEDI in the treatment group, and 2.48% (49/1973) for SEEDI in the control group. There was no significant difference between the incidence rates of the treatment and control group (χ^2=2.40, P>0.05), and the corresponding blocking rate was 33.06%.

There were 61 EC cases diagnosed from the 866 SEEDII cases during the same period, yielding an incidence rate of 7.04% (61/866) for all of the SEEDII, 2.87% (8/279) for SEEDII in the treatment group, and 9.03%(53/587) for SEEDII in the control group. A significant difference was observed between the two incidence rates of the two groups (χ^2=10.00, P<0.01), and the blocking rate of ZSP for SEEDII was 68.22%.

Table 3 Results of blocking treatment of SEEDIand SEEDII cases by ZSP and PLACEBO after three years of medication

SEEDI

Group	No. subjects	No. EC Diagnosed	In cidence Rates (%)	Block Rates (%)
Treatment	1206	20	1.66	
Control	1973	49	2.48	
Total	3179	69	2.17	33.06

SEEDII

Group	No. subjects	No. EC Diagnosed	In cidence Rates (%)	Block Rates (%)
Treatment	279	8	2.87	
Control	587	53	9.03	
Total	866	61	7.04	68.22

DISCUSSION

Dysplasia is an atypical state of the epithelium with a basophilic matrix, a high matrix-core ratio, and hyperheterochromatin. It is historically classified into three grades according to the degree of atypical epithelium in comparision with the basal zone as defined by the World Health Organization's International Histological Classification of Tumors[43]. Atypical cells localized in the basal zone in MEED, while immature cells occupy more than three quadrants of the epithelium in SEEDIand SEEDII.

In this study, we found that 31.92% and 24.15% of people aged 40 years and older in Chixian could been diagnosed as MEED and SEED cases. Qiu and Yang[44] have reported a similar dysplasia rate of 32.28% in people aged 21 years and older in Linxian, which is a neighboring County to Chixian County situated in the same Taihang Mountain area in northern China where there is the highest incidence of EC. However, the rate of dysplasia in low risk regions was only 4.78%, most of the dysplasia belonged to MEED, and the frequency of dysplasia correlated well with the regional level of ECs.

The severity of dysplasia increased with age. As in Table 1, as patients got older, their chances of being detected as one of the dysplasia states grew higher. This was true with MEED, SEED I, and SEEDII. Moreover, the extent of increase in detection rates with age was small for MEED, large for SEEDI, and still larger for SEEDII. The Odds Ratios of the detection rates of the 60-year-old group versus that of the 40-year-old group for MEED, SEEDIand SEEDII were 1.18, 1.61, and 1.80 respectively. This increase with age is remarkably similar to the increase of incidence or mortality of EC with age[46-50], but the degree of the latter was much greater. As in Table 1, the Odds Ratio of detection rates of 60-year-olds against that of 40-year-olds grew up to 2.56 and 5.78 for NEC and EC. It may be suggested that the increase of dysplasia rates with age was small and unstable or reversible for the less severe states such as MEED, but

became fixed and remarkably large as the dysplasia progressed into more severe stages or transformed into NEC and EC.

While the chances of dysplasia increased with age, the total detection rates for MEED, SEEDIand SEEDIIdecreased from 31.92%, 18.98% to 5.17% in the direction of dysplasia development. It may suggest that although dysplasia may proceed further, only a limited portion proceeds into more severe or malignant.

Our finding and discussion so far support the notion that dysplasia belongs to a early form of carcinoma. The main difference between dysplasia and EC may be that dysplasia is an unstable or unfixed state of existence. It may develop further, but much of it will stay unchanged, or even return to normal or less severe again. Therefore, if we could detect and treat precancerous dysplasia lesions before they develop into carcinomas, then the long-term survival of ECs should dramatically improve.

The present study has focused primarily on the blocking treatment of dysplasia cases in high risk populations. The result was that ZSP blocked EC incidence rate by 47.79% after 3 years of medication for the SEED cases. In a previous National Seventh Five Research Project carried out in Linxian County, Lin found that ZSP reduced the EC transformation rate of SEED cases by 52.2% after 3 year medication[24]. These consistent findings by a series of population-based prospective cohort studies in the same high risk area enabled us to conclude that EC is preventable on the secondary blocking treatment level, and ZSP is an effective agent to treat precancerous EC lesions in high risk areas[51-53].

Experimental observations indicate that cancer preventive chemical agents take effect by acting on the promotion stage[25]. The anti-carcinogenicity of certain Chinese herbs is considered to share the same mechanism. In this study, the significant blocking rate of 47.79% by ZSP for the SEED cases resulted mainly from the difference in the registered incidence of EC between the treatment and control groups, as there was no significant difference in the re-screened EC incidence rates between the two groups. As we know, registered EC represents clinically diagnosed late-staged EC, while EC screened out by EBC belonged to the early asymptomatic patients. The finding that ZSP reduced only the registered three year incidence rate, but not the EBC re-screened incidence rate of EC suggests that ZSP may have blocked or delayed the appearance of clinically recognizable EC developed from SEED. In other words, ZSP acted mainly on the late stage of EC development. As in Table 3, the more remarkable blocking rate by ZSP for SEEDIIversus SEEDI(68.22% versus 33.06%) also supports the idea that ZSP was effective in blocking or delaying the appearance of EC during the late stages of EC development.

In a previous comprehensive field prevention and treatment study of esophageal cancer carried out in Linxian county, Lin found that Riboflavin had no significant effect on MEED cases at the end of three years of medication, but a blocking rate of 37.0% appeared at the end of 9 year follow up[24,25]. The result at the end of a three year medication period was the same as in the present study. Further findings will be reported by continuous observation.

In conclusion, we regard dysplasia as a precancerous lesion in people aged 40 years and older in high risk areas. Efforts should be made to screen and treat dysplasia cases before the disease transforms into the irreversible malignant state. Effective screening plus blocking treatment in high risk populations may reduce the mortality rate of EC over the long term. ZSP has been made from natural Chinese herbs which are cheap and share rich resources. Repeated demonstration of its ability will make it a promising agent for secondary prevention of EC.

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Edited by Pagliarini R