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The Effect of Long-term Administration of Korean Red Ginseng in Chinese of Colorectal Adenoma History: A Randomized Controlled Trial

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Research Article

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Abstract

People of colorectal adenoma history are of high risk to progress to colorectal cancer. However, there are no effective drugs to prevent adenoma progressing to cancer in colorectum. In the last century, a promising agent, Panax ginseng was confirmed of anti-carcinogenic properties in animal models and epidemiological studies. This study was to evaluate the effects of red ginseng extract on the incidence of human primary cancer in Chinese of colorectal adenoma history.

Methods: We conducted a randomized, double-blinded, placebo-controlled trial on 572 Chinese of colorectal adenoma history in Haining city, Zhejiang Province, China. Red ginseng extract powder (1g) was specified in terms of its components and administered orally to each patient per week for 3 years and followed up for cancer incidence for 12 years. The development of various cancers in the red ginseng subjects was compared to that of the placebo group. Results. There were 40 cancer cases observed in both two groups in the 12 following-up years, and 5 verse 2 colorectal cancer cases whereas 15 and 18 non-colorectal cancer cases in the placebo and the red ginseng group respectively. The colorectal cancer prevalence in the red ginseng group (2/287) is 2.5 times lower than which in the placebo group (5/285), however, the difference of distribution of cancer type in two groups was of no statistical significance. And 5 stomach cancer cases observed in the red ginseng group and the stomach cancer incidence rate is little higher than which in the placebo group (p=0.047). The cumulative morbidity risk was a little higher in the placebo group than which in the red ginseng group from 2002 through 2011 and reach almost the same level in 2012 in both two groups.

Conclusions: this study hint that the red ginseng extract powder may have some preventive effects on the incidence of cancers in Chinese of colorectal adenoma history except stomach cancer, and it need more sufficient proof from more large sample results to confirm in the future.

Keywords: Cancer Prevention; Colorectal Adenoma; Randomized Control Trail; Red Ginseng

Introduction

It is proved that most colorectal cancers were developed from colorectal adenoma and people of colorectal adenoma history were verified to be and recognized as a high-risk population of colorectal cancer [1-5].

However, there are no effective drugs to prevent adenoma progressing to cancer in colorectum. Colonoscopy can remove adenoma completely but it can't prevent recurrence of adenoma and new appearance in colorectum that may progress to be malignant at later.

In the last century, a promising agent, Panax ginseng was confirmed of anti-carcinogenic properties in animal models [6-9]. Ginsenoside Rg3 (Rg3), a trace tetracyclic triterpenoid saponin, is extracted from ginseng and shown to have anticancer activity against several types of cancers [10], later a significant anti-carcinogenic effect was exerted by 6-year-old red ginseng powder or extract [11]. In human epidemiology research by case-control study, reducing the risk of development of all cancers was reported and a dose-dependent effect was also observed in smoking-related cancers [12]. The red ginseng was confirmed again having a non-organ- specific preventive effect against cancer in two cohort studies [11-13,14]. and the red ginseng was found to have positive inhibition on colorectal cancer cells and patients [15-16]. Based on these finding, we conducted a random control trial to observe whether or not the red ginseng having the preventive effect of cancer occurrence on those of colorectal adenoma history

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Methods

Study design and data collection

A randomized, double-blind, placebo-controlled study was carried out in Haining city, Zhejiang province, China., in July 1997. A total of 577 permanent residents (aged 40-70 years old) of colorectal adenoma history (colorectal adenoma was diagnosed by colonoscopy and confirmed by pathology in the past 10 years) was selected as subjects and randomly divided into ginseng and placebo groups by table of random numbers. Those of family history of cancer and colorectal adenoma, and with personal cancer history were excluded. In the total 576 participants, four participants refused to take any capsules in two weeks later, therefore, 572 participants joined this study and participated in the research and were voluntarily signed an informed consent form. Capsules containing the red ginseng extract powder and placebo prepared by Korea Ginseng Corp, Seoul were purchased and information about the capsules content was not known by the field study team and research designer until all of the result data were collected in 2012. All of the participants were numbered firstly, then the capsules were distributed to them by randomization of using a table of randomly assorted digits. The study consisted of 3 years of intervention (1997 - 2000) and 12 years of follow-up (2001-2012). Each participant was administered with four capsules of ginseng extract powder or placebo(1g) every week from July 1997 to June 2000 with the delivery of one-month capsules. Participants were asked to complete questionnaires by face-to-face interview about these contents: demographic characteristics, occupation, smoking and alcohol drinking patterns, history of diseases, and history of ginseng intake at the beginning of the study, and were also asked to take any kinds of ginseng during the periods of 1997-2000. The participants were followed up for cancer occurrences and deaths for 12 years (from January ,2001 to December 30, 2012) after 3 years of intervention by telephone every year, and all new cancer cases were verified again through the local cancer registration system. At the end of this study, 12 years from the beginning of this trial, the identities of individual subjects were opened and confirmed. and 285 subjects were randomized to the placebo group whereas 287 to red ginseng group.

Statistical Analysis

The Relative Risks (RRs) were estimated by logistic regression models. Age distribution and duration of red ginseng intake were using t-test. The rate in both groups was analyzed by x^2.

Results

Sample characteristics

Of the 572 participants, 287 subjects took red ginseng whereas 285 subjects took a placebo. The sex, age, BMI (Body Mass Index), history of smoking, alcohol drinking and ginseng intake distribution were similar between the two groups, and the duration of capsule intake was also of no statistical difference in both groups (Table1).

Overall cancer occurrence observed in two groups

There were 40 cancer cases observed in both two groups in the following-up years, and 5 verse 2 colorectal cancer cases in placebo and red ginseng groups respectively whereas 15 and 18 non-colorectal cancer cases in each group (Table 2).

In the 40 cancers, there were 11 lung cancer cases(27.5%), 7 colorectal cancer cases(17.5%), 5 liver cancer cases(12.5%) and stomach cancer cases(12.5%), 3 esophageal cancer cases(7.5%), 2 pancreatic cancer cases(5.0%) and mouth cancer cases(5.0%), and 1 each case for gallbladder cancer case (2.5%), urinary bladder cancer(2.5%), peritoneal interstitial tumor case (2.5%), ovarian cancer case (2.5%) and bone marrow cancer case (2.5%) (Table 3).

Comparison of the cancer occurrence in two groups

There are 5 stomach cancer cases observed in the red ginseng group and the stomach cancer incidence rate is higher than which in the placebo group (p=0.047, Table 3).

The red ginseng decreased the risk for development of cancer only in women (RR=0.36, 95%CI, 0.07-1.85) and in the duration red ginseng intake of 53-104 weeks (RR=0.25, 95%CI, 0.44-1.43) compared to placebo group, whereas the RR is little higher in red ginseng group in man and in the longest duration of red ginseng intake (105-156 weeks), but all of these difference is of no statistical significance (Table 4).

Table 1:

	Placebo (%)	Red Ginseng (%)	Total (%)	P value
Sex				
Male	187(65.6)	179(62.2)	366(64.0)	0.388
Female	98(34.4)	108(37.8)	206(36.0)	
Age				
40-49	31(10.9)	30(10.5)	61(10.7)	0.929
50-59	154(54.0)	159(55.4)	313(54.7)	
60-69	79(27.7)	74(25.8)	153(26.7)	
70-79	21(7.4)	24(8.4)	45(7.9)	
mean	57.10±7.38	57.31±7.53		0.744
Smoking				
Nonsmoker	131 (46.0)	140 (48.8)		0.504
Smoker	154 (54.0)	147 (51.2)		
Alcohol drinking				
Nondrinker	142 (49.8)	129 (44.9)		0.276
Drinker	143 (51.2)	158 (55.1)		
Body mass index (kg=m^2)				
≤18.4	31 (10.9)	24 (8.4)		0.591
18.5-22.9	167 (58.6)	174 (60.6)		
≥23.0-	87 (31.3)	89 (31.0)		
History of ginseng intake				
No	99 (34.7)	107 (37.3)		0.543
Yes	186 (65.3)	180 (52.8)		
Duration (weeks) of capsules Intake				
	146.24±27.82	149.81±23.96		0.144
Cancer (No)	265 (93.0)	267 (93.0)	532 (93.0)	0.982
Cancer (Yes)	20 (7.0)	20 (7.0)	40 (7.0)	
Total	285 (10.00)	287 (100.0)	572 (100.0)	

Table 2: Cancer and duration (weeks) of capsules intake distribution in two groups and RRs (95% CI) of Cancer.

Variable	Placebo (%)	Red Ginseng (%)	RR (95%CI)	p-Value
New Cancer cases in both sexes				
No cancer	265(93.0)	267(93.0)	1	0.407*
Cancer	20(7.0)	20(7.0)	0.99(0.52-1.89)	
Colorectal cancer	5(1.8)	2(0.7)		
Non-colorectal cancer	15(5.3)	18(6.3)		
In Male				
No cancer	172(92.0)	161(89.9)	1	0.639*
Cancer	15(8.0)	18(10.1)	1.28(0.63-2.63)	
Colorectal cancer	3(1.6)	2(1.1)		
Non-colorectal cancer	12(6.4)	16(8.9)		
In Female				
No cancer	93(94.9)	106(98.1)	1	0.238*
Cancer	5(5.1)	2(1.9)	0.36(0.07-1.85)	
Colorectal cancer	1(1.0)	0	0	
Non-colorectal cancer	4(4.1)	2(1.9)		
Duration (weeks) of capsules intake				
≤52	12(4.2)	8(2.8)	1	
53-104	12(4.2)	2(0.7)	0.25(0.44-1.43)	
105-156	261(91.6)	277(96.5)	1.59(0.64-3.96)	

*The p values of Fisher exact x^2 are calculated between colorectal cancer and Non-colorectal cancer groups by sex.

Table 3: Histopathological diagnosis of 40 cancer cases in both groups by sex.

Histopathological Diagnosis	Case Number (%)						Total	*p value**
	Placebo			Red Gingseng				
	Male	Female	Total	Male	Female	Total		
Colorectal cancer	4(57.1)	1(14.2)	5(71.4)	2(28.6)	0	2(28.6)	7(100.0)	0.731
Lung cancer	3(27.3)	1(9.1)	4(36.4)	7(63.7)	0	7(63.7)	11(100.0)	0.48
Liver cancer	2(40.0)	0	2(40.0)	3(60.0)	0	3(60.0)	5(100.0)	1
Stomach cancer	0	0	0	5(100.0)	0	5(100.0)	5(100.0)	0.047
Esophageal cancer	0	1(50.0)	1(50.0)	0	1(50.0)	1(50.0)	2(100.0)	1
Pancreatic cancer	1(50.0)	1(50.0)	2(100.0)	0	0	0	2(100.0)	0.487
Mouth cancer	1(50.0)	1(50.0)	2(100.0)	0	0	0	2(100.0)	0.487
Gallbladder cancer	1(50.0)	1(50.0)	1(100.0)	0	0	0	1(100.0	1
Urinary bladder cancer	1(100.0)	0	1(100.0)	0	0	0	1(100.0)	1
Peritoneal interstitial tumor	0	0	0	1(100.0)	0	1(100.0)	1(100.0)	1
Ovarian cancer	0	0	0	0	1(100.0)	1(100.0)	1(100.0)	1
Bone marrow cancer	1(100.0)	0	1(100.0)	0	0	0	1(100.0)	1
Total Number	**14(35.0)**	**6(115.0)**	**20(50.0)**	**18(45.0)**	**2(5.0)**	**20(50.0)**	**40(100.0)**	**0.982****

*The p values of Fisher exact x^2 are calculated between the placebo and red ginseng groups (**p values of Pearson x^2).

Table 4: Accumulative morbidity risk of all cancers from 1998 through 2012 within the both groups.

Year	Placebo group(n=285)			Red Ginseng group (n=287)		
	Number of cases	Morbidity Rate (%)	Accumulative Morbidity rate (%)	Number of cases	Morbidity Rate (%)	Accumulative morbidity rate (%)
1998	2	0.7	0.7	1	0.35	0.35
1999	4	1.4	2.1	2	0.7	0.7
2000	0	0	2.1	4	1.4	1.4
2001	1	0.35	2.45	1	0.35	2.8
2002	4	1.4	3.85	2	0.7	3.15
2003	2	0.7	4.55	1	0.35	3.85
2004	3	1.05	5.6	2	0.7	4.2
2005	0	0	5.6	0	0	4.2
2006	0	0	5.6	1	0.35	4.9
2007	0	0	5.6	0	0	5.25
2008	0	0	5.6	1	0.35	5.25
2009	1	0.35	5.95	1	0.35	5.6
2010	1	0.35	6.3	1	0.35	5.95
2011	1	0.35	6.65	1	0.35	6.2
2012	1	0.35	7	2	0.7	6.55
Total	**20**			**20**		

The colorectal cancer prevalence in the red ginseng group (2/287) is 2.5 times lower than that in the placebo group (5/285), however, the difference of distribution of cancer type in two groups was of no statistical significance. The cumulative morbidity risk was a little higher in the placebo group than which in the red ginseng group from 2002 to 2011 and became almost the same level in 2012 in both two groups (Table 4 and Figure 1).

Discussion

Colorectal cancer is increasing quickly in China and will be a great burden to China government and patients. Except for screening, there are of no effective methods to reduce colorectal cancer mortality.

From previous studies, patients perceived to be at increased risk of colorectal neoplasm after adenoma removal are recommended surveillance colonoscopy [2-4]. Cottet V., reported that the 10-year cumulative probabilities of colorectal cancer were 2.05% (95% CI 1.14% to 3.64%) and 6.22% (95% CI 4.26% to 9.02%) in those of non-advanced adenoma and advanced adenoma history respectively [17]. CRC mortality of individuals who had adenoma removed was 237/10,000 in Sweden and Norwegian and 208/10,000 in UK [18,19], which is much higher than the general population.

From 2019, the China government issue “health China action” which including preventing cancer effectively at an early stage. Colorectal adenoma especially advanced adenoma is of high probability to develop to cancer; therefore, colorectal adenoma is the target disease of the prevention of colorectal cancer, and we defined individuals who had adenoma removed as the high-risk population of colorectal cancer and the target prevention population.

Up till now, there are no effective methods and drugs to prevent the colorectal adenoma except colonoscopy of the adenoma. Colonoscopy can remove most colorectal adenoma but it cannot prevent its recurrence and appearance. If there is a drug that can inhibit the occurrence and recurrence of colorectal adenoma, the colorectal cancer incidence will decrease rapidly and the burden from colorectal cancer will also decline. The Panix ginseng is expected to have the preventive effect of colorectal adenoma to cancer for the animal experiments and some epidemiological studies [20-22].

However, there is no obvious cancer-preventive effects observed in this study. The sex and age distribution were of no difference between red ginseng and placebo groups. There are 20 new cancer cases in the red ginseng group (287 participants, who taking ginseng) and 20 new cancer cases in the placebo group (285 participants, who took placebo) respectively in the next 14 following-up years, and the accumulated cancer incidence is almost the same in two groups (Table1). There were 5 verse 2 colorectal cancer cases in placebo and red ginseng groups respectively whereas 15 and 18 non-colorectal cancer cases in each group (Table 2).

There are 5 stomach cancer cases observed in the red ginseng group and the stomach cancer incidence rate in the red ginseng group is little higher than which in the placebo group with a boundary level of significance (p=0.047) (Table 3).

Other types of cancer cases distribution between the two groups were of no significance. This result implies that the long-term taking of red ginseng having the probability of increased risk of suffering stomach cancer in Chinese of colorectal adenoma history. However, in our previous RCT results, there was no difference of stomach cancer prevalence in Chinese of chronic atrophic gastritis patients in the red ginseng and placebo group [11]. The accumulative morbidity curves of all cancers in the red ginseng group was observed a little lower than which in the placebo group after taking ginseng for two or three years from 2002 through 2011 and became almost the same level in 2012 in both two groups (Table 4 and figure 1), which means that the red ginseng taking may decrease the risk of suffering cancer and the preventive effects will vanish in 10 years. For this study sample is not large enough, the decease of the risk of suffering cancer needs more evidence such as more larger sample random trial results to support it in the future.

Conclusion

In this study, the accumulative morbidity curves of all cancers in the red ginseng group was observed a little lower than which in the placebo group from 2002 through 2012, and the stomach cancer incidence rate in the red ginseng group is little higher than which in the placebo group with a boundary level of significance. the results hint that the red ginseng extract powder may have some preventive effects on the incidence of cancers in Chinese of colorectal adenoma history except stomach cancer, however, this result is not enough to confirm the preventive effects and more sufficient proofs from more large samples results are needed in the future.

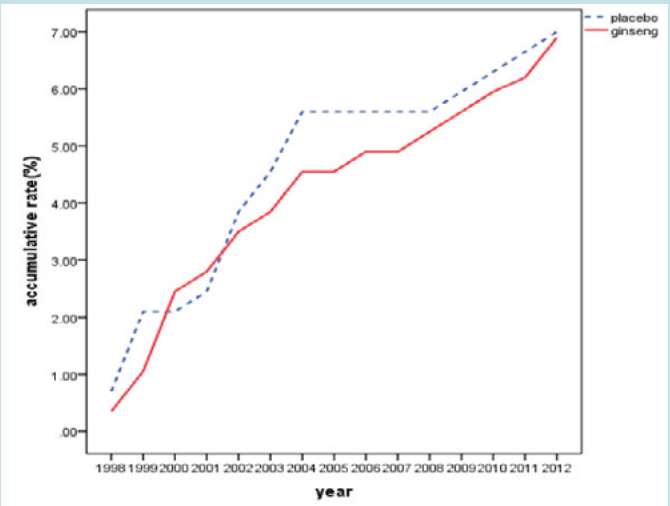

Figure 1: Accumulative morbidity risk of all cancers during the period of 1998-2012 in both groups.

Conflicts of Interest

This study was also approved by the ethics committee of the Second Affiliated Hospital, College of Medicine, Zhejiang University in 1998. The authors declare that they have no competing interests.

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