

Non-organ specific cancer prevention of ginseng: a prospective study in Korea

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- Background** A number of studies have reported that increased consumption of natural products reduced the risk of cancer. Our previous case-control studies have shown a significant reduction in the risk of cancer development among those who regularly consumed ginseng. We conducted a prospective cohort study to evaluate the preventive effect of ginseng against cancer on a population residing in a ginseng cultivation area on the basis of the result of case-control studies.
- Methods** This study was conducted in Kangwha-eup from August 1987 to December 1992. We studied 4634 people over 40 years old who completed a questionnaire on ginseng intake. In an attempt to obtain detailed information about ginseng intake, we asked them to specify their age at initial intake, their frequency and duration of ginseng intake, the kind of ginseng, etc. Multiple logistic regression was used to estimate relative risks (RR) when controlling simultaneously for covariates.
- Results** Ginseng consumers had a decreased risk (RR = 0.40, 95% confidence interval [CI] : 0.28–0.56) compared with non-consumers. On the type of ginseng, the RR was 0.31 (95% CI : 0.13–0.74) for fresh ginseng extract consumers and 0.34 (95% CI : 0.20–0.53) for consumers of multiple combinations. There was no cancer death among 24 red ginseng consumers. There was a decreased risk with a rise in the frequency of ginseng intake, showing a dose-response relationship. The RR of ginseng consumers were 0.33 (95% CI : 0.18–0.57) in gastric cancer and 0.30 (95% CI : 0.14–0.65) in lung cancer. Among ginseng preparations, fresh ginseng extract consumers were significantly associated with a decreased risk of gastric cancer (RR = 0.33, 95% CI : 0.12–0.88).
- Conclusions** These results strongly suggest that Panax ginseng C.A. Meyer has non-organ specific preventive effect against cancer, providing support for the previous case-control studies.
- Keywords** Non-organ specific prevention, chemoprevention, ginseng, Panax ginseng C.A. Meyer, cohort study
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Fifty years have already passed since alkylating agents were first developed as cancer chemotherapeutics,¹ but many cancers still remain difficult to cure.² The failure to improve from 1 in 3 in the 1960s to 1 in 2 in the 1970s of 5-year 'observed' survival stimulated awareness of the importance of chemoprevention and researchers have been trying to discover non-toxic cancer chemopreventive agents among natural products.³

We hypothesized that the life-prolongation effect of ginseng described by Shennong⁴ during the Liang Dynasty in China may be due to the preventive activity of ginseng against the

development of cancers. The species of ginseng are Panax ginseng C.A. Meyer (Korean ginseng), which is cultivated in Korea, Japan, China, and Russia; Panax quinquefolius L. (American ginseng), which is raised in the eastern United States and Canada; Panax japonicus C.A. Meyer (Japanese ginseng), which is also called Bamboo ginseng; and Panax notoginseng (Burk) F.H. Chen (Sanchi-ginseng), a native of southwest China (Yunnan and Kwangsi Provinces).⁵ In Korea, Kangwha, Keumsan and Punggi areas are the locations suited to ginseng production. We carried out extensive animal experiments to investigate whether Panax ginseng C.A. Meyer (Korean ginseng) inhibited carcinogenesis, and demonstrated that red ginseng extract had an anticarcinogenic effect against pulmonary tumours induced by chemical carcinogens in long-term^{6,7} and medium-term anticarcinogenesis models using mice.^{8–11} We further investigated whether fresh ginseng has similar anticarcinogenic effects using

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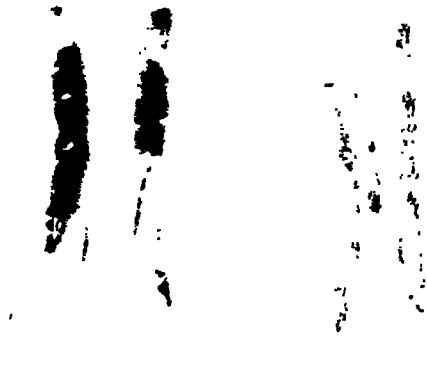


Figure 1 Panax ginseng C.A. Meyer in Korea are classified into fresh ginseng (left), white ginseng (centre) and red ginseng (right)

Yun's 9 weeks medium-term anticarcinogenicity test.^{12,13} A significant anticarcinogenic effect was observed in 6-year-old dried powder or extracted fresh ginseng; 5- and 6-year-old white ginseng powder or extract; 4-, 5-, and 6-year-old red ginseng powder or extract.

It has been shown that ginseng inhibited liver cancer induced by diethylnitrosamine in rats.¹⁴ It has also been reported that tissue culture biomass tincture obtained from culture cells of Panax ginseng C.A. Meyer had a marked inhibitory effect on adenocarcinoma induced by *N*-methyl-*N*-nitrosourea administration in rats.¹⁵

In 1987, we began to conduct a case-control study of 905 pairs¹⁶ to confirm whether red ginseng extracts had as much anticarcinogenic effect as in mice. We extended the number of subjects for a case-control study to 1987 pairs¹⁷ from 905 pairs. The results showed a dose-response relationship in ginseng consumers and a marked decrease in risk for consumers of ginseng extracts and red ginseng, showing agreement with the effect observed in animal experiments.

The aim of the prospective study is to investigate whether ginseng intake is related to the mortality and morbidity of various cancers and to evaluate the preventive effect of ginseng in the population residing in ginseng cultivation area 6 months (in August 1987) after the first case-control study.

Subjects and Methods

The study population was selected from people who were listed in the 1987 residents list registered at the provincial government offices of the ginseng production areas. These lists contain the name, sex, date of birth, permanent and present addresses.

Subjects born before 1947 (over 40 years) were selected. A cohort of 4634 people over 40 years age residing in Kangwha-eup was interviewed and examined between August 1987 and December 1989 in order to investigate the preventive effect of ginseng on cancer.

Each study subject was interviewed by means of a standard questionnaire about demographic characteristics, lifelong occupation, smoking and drinking habits, past history of diseases, etc. In an attempt to obtain detailed information about ginseng intake, we asked them to specify their age at initial intake, frequency and duration of ginseng intake, the kind of ginseng, etc. Ginseng types were classified into fresh ginseng, white ginseng and red ginseng (Figure 1). Fresh ginseng is less than 4 years old and can be consumed as it is. White ginseng is grown for 4–6 years, and then peeled and dried to reduce the water content to 12% or less. Red ginseng is harvested after 6 years, and then steamed and dried. Each type of ginseng is further categorized into several products. In the case of fresh ginseng, the categories include fresh sliced (thinly sliced pieces taken with or without honey), fresh extract (ginseng soup boiled for more than 3 hours), boiled young fresh ginseng root with chicken, etc. For white ginseng, the categories include powder (white ginseng in powder form), extract (boiled white ginseng soup), tea, etc. Red ginseng was classified into extract (boiled red ginseng soup), powder, etc. In addition, multiple combinations among fresh, white and red ginseng etc. were included. Interviews on ginseng intake were carried out by asking the following serial questions in order to exactly characterize lifelong ginseng intake; 1) Have you ever consumed ginseng? 2) At what age did you take ginseng for the first time? 3) What type of ginseng products have you taken? and 4) How often (frequency) and for how

long (duration) have you used it? The frequency of ginseng intake was divided into four categories: no intake, 1–3 times per year, 4–11 times per year and more than once a month (12 times or more per year). All interviews were conducted by 10 trained personnel, usually in the home of the subjects. These interviewers had been instructed and trained beforehand to ensure uniformity in the method of enquiry. They collected information by using a precoded questionnaire that took approximately half an hour to complete.

We carried out follow-up studies on all cohort members to document the development of cancer and other illnesses and to update exposure information. Length of follow-up was calculated for each individual in the study as the number of days elapsed since completion of the questionnaire until death from cancer or other diseases. Deaths among the cohort from August 1987 to December 1992 were traced by population registration cards with no follow-up loss. A cohort member was classified as a cancer case if they had any disease code of cancer in hospital records, death certificates of the provincial government, prevalence data of the Korea Medical Insurance Corporation, etc. The diseases were classified by the first three digits of the International Classification of Diseases.¹⁸ The total number of subjects interviewed was 4675. Among them 41 prevalent cancer cases were excluded. This left 4634 eligible subjects (2362 men and 2272 women) for analysis. During the period, 7.7% (355 of 4634) of the subjects had died. Cancer accounted for 137 (3.0%), with 58 (1.3%) alive and 79 (1.7%) deaths. There were 229 (64.5%) deaths due to other diseases; 47 subjects with unknown diseases were excluded. This left 4587 study eligible subjects for relative risk analyses.

The Mantel-Haenszel procedure was used to estimate the relative risk (RR) of ginseng intake adjusted by age and sex.^{19,20} The possibility of a linear trend in risk across exposure categories was tested by a trend statistic. Multiple logistic regression was used to control simultaneously for the effects of risk factors. All the regression equations included terms for age (three categories), sex, education (years of schooling grouped into four categories), smoking and alcohol consumption. Data analyses were done by PC-SPSS version 6.1 statistical package.²¹

Results

The distribution of demographic and social characteristics for subjects residing in Kangwha-eup is shown in Table 1. The average age at interview was 54.2 for males and 56.9 for females. Buddhism was the most common religion. Females generally had fewer years of schooling, were more often widowed, and were from a lower social class than males.

Of 4634 people eligible for analysis, 70.5% (3267) were ginseng consumers (Table 2). Ginseng consumers had a decreased risk (RR = 0.40, 95% CI : 0.28–0.56) for cancer compared with non-consumers (Table 3). On the type of ginseng, the RR of cancer was 0.31 (95% CI : 0.13–0.74) for fresh ginseng extract consumers. The RR for other types of ginseng showed a decreasing trend, but it was not statistically significant.

There was a decreased risk with the frequency of ginseng consumed, showing a statistically significant dose-response relationship (Table 4). The RR ranged from 0.46 of those who had consumed ginseng less than three times per year to 0.34 to those who had consumed more than once per month. During

Table 1 Per cent distribution of demographic and social characteristics for subjects

Variables	Male	Female	Total
No. of studied population	2362	2272	4634
Age group			
40–49	39.4	31.3	35.4
50–59	32.0	31.2	31.6
60–69	18.6	21.2	19.9
70–79	8.7	11.3	10.0
80–	1.3	5.0	3.1
Mean age (years)	54.2	56.9	55.5
Marital status			
Married	90.0	68.8	79.6
Widowed	7.5	29.0	18.1
Other	2.5	2.2	2.3
Religion			
None	45.8	39.8	42.8
Buddhist	24.3	27.7	26.0
Protestant	17.9	19.4	18.6
Catholic	5.5	6.3	5.9
Confucianism	5.1	4.7	4.9
Other	1.4	2.1	1.8
Education			
None	15.1	38.9	26.8
Primary school	38.6	45.1	41.8
Middle school	23.7	12.2	18.0
High school	19.0	3.3	11.3
College and above	3.6	0.5	2.1
Occupation			
Professional and technical workers	2.8	0.2	1.5
Administrative workers	0.2	0.1	0.1
Clerical workers	6.2	0.4	3.4
Service workers	6.6	1.2	4.0
Sales workers	18.3	11.9	15.2
Agricultural workers	37.2	27.9	32.6
Production workers and labourers	5.1	2.3	3.7
No occupation	23.6	56.0	39.5

the study period, 137 cancer cases were diagnosed as cancers including 42 stomach, 24 lung, 14 liver and 57 at other sites (Table 5). The RR of ginseng consumers were 0.33 (95% CI : 0.18–0.57) for gastric cancer and 0.30 (95% CI : 0.14–0.65) for lung cancer, showing statistical significance (Table 6). Among ginseng preparations, only fresh ginseng extract consumers were associated with a decreased risk of gastric cancer (RR = 0.33, 95% CI : 0.12–0.88), but other types of ginseng showed a decreasing trend.

Discussion

This cohort study was carried out on the population of over 40-year-olds residing in Kangwha-eup in August 1987 immediately after confirming preliminary results of the case-control studies. Kangwha-eup is one of the four large ginseng cultivation areas, the core of which is Kangwha island located on the

Table 2 Distribution of ginseng intake by subjects

Type of ginseng	Male	Female	Total
Studied population	2362 (100.0)	2272 (100.0)	4634 (100.0)
No intake of ginseng	578 (24.5)	789 (34.7)	1367 (29.5)
Intake of ginseng	1784 (75.5)	1483 (65.3)	3267 (70.5)
Fresh ginseng			
Sliced	139 (5.9)	108 (4.8)	247 (5.3)
Extract	150 (6.4)	156 (6.9)	306 (6.6)
Sliced & extract	42 (1.8)	40 (1.9)	82 (1.8)
Sliced & tea	217 (9.2)	136 (6.0)	353 (7.6)
Extract & white ginseng extract	7 (0.3)	10 (0.4)	17 (0.4)
Extract & powder	33 (1.4)	17 (0.7)	50 (1.1)
White ginseng			
Extract	33 (1.4)	37 (1.6)	70 (1.5)
Extract & sliced	57 (2.4)	34 (1.5)	91 (2.0)
Powder	94 (4.0)	58 (2.6)	152 (3.3)
Powder & sliced	40 (1.7)	31 (1.4)	71 (1.5)
Extract & powder	6 (0.3)	4 (0.2)	10 (0.2)
Tea	282 (11.9)	182 (8.0)	464 (10.0)
Red ginseng			
Extract	15 (0.6)	9 (0.4)	24 (0.5)
Extract & sliced	9 (0.4)	2 (0.6)	21 (0.5)
Fresh ginseng extract	2 (0.1)	5 (0.2)	7 (0.2)
Extract & powder	3 (0.1)	3 (0.1)	6 (0.1)
Boiled chicken with young ginseng root	177 (7.5)	220 (9.7)	397 (8.6)
Other combinations	478 (20.1)	421 (18.3)	899 (19.3)

Values in parentheses are percentages.

side of the West Sea (Yellow Sea) and is 30 minutes' drive from Seoul.

Of 4634 people eligible for analysis, excluding 47 unknown diseases, 54.7% of the 137 cancer cases had a history of ginseng intake in comparison with 71.2% of 4450 non-cases. This showed similar results compared with those of the proportion (74.5% and 69.6%) of control groups in the previous case-control studies.^{16,17} The present study found a significant reduction of RR (0.39) between the intake of ginseng and cancer, as shown in the previous studies (OR = 0.56 and 0.50). On the type of ginseng, the RR of cancer were significantly reduced for fresh ginseng extract consumers and consumers with multiple combinations. The RR for other types of ginseng including white ginseng tea showed a decreasing trend, but this was not statistically significant. Among 24 red ginseng consumers, there were no deaths from cancer. This study did not show any relationship between fresh ginseng consumers and cancer, which is consistent with the experimental study^{12,13} and case-control studies.^{16,17}

For cancer sites, among 137 cancer patients during the 5-year follow-up period, there were 42 (30.6%) cases of stomach cancer; 24 (17.5%) for lung cancer and 14 (10.2%) for liver cancer. This was similar to the mortality rates for cancers of stomach, liver and lung in Korea.²² The RR of ginseng consumers were 0.33 (95% CI : 0.19–0.60) for gastric cancer and 0.30 (95% CI : 0.14–0.65) for lung cancer. Among ginseng preparations, fresh ginseng extract consumers were significantly associated with a decreased risk of gastric cancer (RR = 0.33, 95% CI : 0.12–0.88). The results showed that ginseng intake had a preventive effect against cancers of the stomach and lung in spite of different mechanisms of histogenesis or carcinogenesis, and aetiological aspects.

In case-control studies for 905 pairs and 1987 pairs, there was a notable decrease in risk for intake of ginseng extract compared to intake of fresh ginseng and there was a dose-response relationship according to frequency of ginseng intake. The OR of ginseng consumers decreased in all kinds of cancers. The Lancet²³ stated in an editorial that although organ-specific

Table 3 Relative risks of cancer by ginseng intake

Kind of ginseng	No. of subjects	No. of cancer cases	RR ¹	95% CI	RR ²	95% CI
No intake	1283 (6457) ^a	62 (9.6) ^b	1.00	–	1.00	–
Ginseng intake	3167 (15 947)	75 (4.7)	0.48	0.34–0.67	0.40	0.28–0.56
Fresh ginseng						
Sliced, juice	236 (1166)	8 (6.9)	0.66	0.32–1.39	0.67	0.33–1.32
Extract	296 (1334)	3 (2.2)	0.23	0.08–0.63	0.31	0.13–0.74
White ginseng						
Powder	147 (652)	5 (6.1)	0.59	0.22–1.62	0.49	0.19–1.23
Extract	68 (377)	1 (2.7)	0.62	0.15–2.53	0.50	0.12–2.07
Tea	442 (2331)	18 (7.7)	0.89	0.52–1.52	0.65	0.37–1.12
Red ginseng extract	24 (125)	–	–	–	–	–
Boiled chicken with young ginseng root	381 (1907)	12 (6.3)	0.77	0.40–1.23	0.71	0.38–1.21
Multiple combinations	1573 (8055)	28 (3.5)	0.37	0.24–0.57	0.34	0.20–0.53

RR¹ Adjusted for age and sex.

RR² Adjusted for age, sex, education, smoking and alcohol consumption.

()^a Person-years of follow-up.

()^b Incident rate for 1000 person-years.

Table 4 Relative risks of cancer by frequency of ginseng intake

Times of ginseng intake	No. of non-cases	No. of cancers	RR ¹	95% CI	RR ²	95% CI
No intake	1283	62	1.00	-	1.00	-
1-3 times/year	1439	39	0.54	0.36-0.82	0.46	0.30-0.69
4-11 times/year	924	21	0.49	0.30-0.79	0.35	0.21-0.58
Once/month or more	804	15	0.41	0.24-0.71	0.34	0.20-0.59

RR¹ Adjusted for age and sex.

RR² Adjusted for age, sex, education, smoking and alcohol consumption

Table 5 Distribution of confirmed cases for cancer and other diseases

Disease	No. alive	No. of deaths	Total
All cancers	58	79 (22.3)	137
Oral cavity and pharynx	1	1	2
Oesophagus	1	2	3
Stomach	20	22	42
Colon	-	1	1
Rectum	4	2	6
Liver	4	10	14
Pancreas	-	3	3
Larynx	-	4	4
Lung	4	20	24
Leukaemia	2	2	4
Female breast	8	1	9
Cervix uteri	2	2	4
Ovary	1	-	1
Urinary bladder	1	1	2
Thyroid gland	1	-	1
Malignant lymphoma	5	1	6
Other cancers	4	7	11
Other diseases	-	229 (64.5)	229
Unknown	-	47 (13.2)	47
Total	58	355 (100.0)	

Values in parentheses are percentages.

approaches to cancer screening and prevention have been the main focus of attention, they make little impact on lung, colon, stomach and liver cancer, which are major killers worldwide. What is needed is more research into non-organ specific strategies. A case-control study of more than 600 individuals from South Korea, which suggested that ginseng consumption reduced risks for all cancer types, is an example of such an approach, but unfortunately the analysis did not include social class as a variable. In response to this, we carried out further statistical analysis on the 905 pairs to evaluate the role of social class as a confounder.

The OR of ginseng consumers adjusted by economic status was 0.57 (95% CI : 0.47-0.70) compared with non-consumers. The distribution of ginseng intake by economic status was 32.8% for low grade, 30.2% for middle grade and 32.1% for high grade, respectively. There was no significant relationship between ginseng intake by economic status. In conclusion, ginseng intake can be considered as a non-organ specific cancer preventive.

Putting the present study and previous two case-control studies together, showed the non-organ specific preventive effect of *Panax ginseng* C.A. Meyer against cancer.

This cohort removed selection and information biases from the case-control studies reported in 1990 and 1995. This study also showed a decreasing risk for cancers of the stomach and lung due to ginseng intake in the results of case-control studies. However, there were no significant differences among other cancers. Our follow-up lasted about 5 years which is not enough to obtain cancer incidence and mortality figures, but the follow-up is continuing. The drawback in our methodology

Table 6 Relative risks of selected cancers by ginseng intake

Ginseng Intake	No. of subjects	Stomach (42)			Lung (24)			Liver (14)		
		No.	RR	95% CI	No.	RR	95% CI	No.	RR	95% CI
No intake	1283	23	1.00	-	14	1.00	-	4	1.00	-
Ginseng intake	3167	19	0.33	0.18-0.57	10	0.30	0.14-0.65	10	0.86	0.25-2.94
Fresh ginseng										
Sliced, juice	236	2	0.57	0.17-1.94	1	0.67	0.15-3.43	2	1.97	0.34-2.95
Extract	296	1	0.33	0.12-0.88	1	0.28	0.04-2.17	-	-	-
White ginseng										
Powder	147	1	0.24	0.03-1.84	-	-	-	-	-	-
Extract	68	2	1.34	0.30-5.97	-	-	-	-	-	-
Tea	442	6	0.64	0.26-1.61	4	0.80	0.26-2.44	2	1.72	0.36-8.26
Boiled chicken with young ginseng root	381	5	0.43	0.12-1.43	1	0.35	0.08-1.95	1	0.85	0.15-4.87

Adjusted for age, sex, education, smoking and alcohol consumption

Values in parentheses indicate number of cancer cases.

was the inability to adjust for potential confounding variables for studied cancers, particularly those related to diet for stomach cancer and HBV for liver cancer. The RR for ginseng intake, adjusted for smoking, decreased lung cancer significantly.

In the case-control study of the 905 pairs, we evaluated the role of social class as a confounder. The OR of ginseng consumers adjusted for economic status were 0.57 (95% CI : 0.47–0.70) compared with non-consumers. The distribution of ginseng intake by economic status was 32.8% for low grade, 30.2% for middle grade and 32.1% for high grade, respectively. Information on economic status of participants was not surveyed in this study, but there were no differences according to education level and occupation between ginseng consumers and non-consumers.

In conclusion, these results revealed that *Panax ginseng* C.A. Meyer has a non-organ specific preventive effect against cancer, providing support for the previous case-control studies.

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