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Epidemiological Study on Cancer Prevention by Ginseng: Are All Kinds of Cancers Preventable by Ginseng?

In the light of experimental results, two case-control studies and one cohort study in a population of ginseng cultivation area were conducted to confirm whether ginseng has any anticarcinogenic effect on human cancers. All participants were interviewed using a standardised questionnaire to obtain the information on demographics, cigarette smoking, alcohol consumption and ginseng intake. In 905 pairs case-control study, 62% had a history of ginseng intake compared to 75% of the controls, a statistically significant difference ($p<0.01$). The odds ratio (OR) for cancer in relation to ginseng intake was 0.56. In extended case-control study with 1987 pairs, the ORs for cancer were 0.37 in fresh ginseng extract users, 0.57 in white ginseng extract users, 0.30 in white ginseng extract users, 0.30 in white ginseng powder users, and 0.20 in red ginseng users. Those who took fresh ginseng slices, fresh ginseng juice, and white ginseng tea, however, did not show decrease in the risk. Overall, the risk decreased as the frequency and duration of ginseng intake increased. With respect to the site of cancer, the ORs for cancers of the lip, oral cavity, pharynx, esophagus, stomach, colorectum, liver, pancreas, larynx, lung and ovary were significantly reduced by ginseng intake. Smokers with ginseng intake showed lower ORs for cancers of lung, lip, oral cavity and pharynx and liver than those without ginseng intake. In 5 yr follow-up cohort study conducted in the ginseng cultivation area, Kangwha-eup, ginseng intakers had significantly lower risk than non-intakers. As for the type of ginseng, cancer risk significantly decreased among intakers of fresh ginseng extract, alone or together with other ginseng preparations. Among 24 red ginseng intakers, no cancer death occurred during the follow-up period. The risk for stomach and lung cancers was significantly reduced by ginseng intake, showing a statistically significant dose-response relationship in each follow-up year. In conclusion, *Panax ginseng* C.A. Meyer has been established as non-organ specific cancer preventive, having dose response relationship. These results warrant that ginseng extracts and its synthetic derivatives should be examined for their preventive effect on various types of human cancers.

Key Words : *Panax ginseng C.A. Meyer; Case-Control Studies; Cohort Studies; Neoplasms; Prevention and control; Anticarcinogenic Agents*

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> And the earth brought forth grass, and herb yields seed according to its kind, and the tree that yields fruit, whose seed is in itself according to its kind. And God saw that it was good.
>
> *Genesis 1 :12 - Old Testament*

INTRODUCTION

The ginseng root has been used empirically for thousands of years in Asian countries. Since 1965, several pharmacological activities of ginseng extracts or ginseng dammarane saponin have been reported, including effects on the central nervous system, antipsychotic action, tranquillizing effects, protection from stress ulcers, increase of gastrointestinal motility, antifatigue action, endocrinological effects, enhancement of sexual behavior, acceleration of metabolism, syntheses of carbohydarates, lipids, RNA, and proteins (1-4).

The ginseng plant is deciduous perennial belonging to the Araliaceae family. Of the 13 species (5, 6), the most prominent are *Panax ginseng* C.A. Meyer, which is cultivated in Korea, Japan, China, Russia, the United States of America, and Germany, *P. quinquefolius* L. (American ginseng) found

in southern Canada and the U.S.A., and *P. japonicus* C.A. Meyer (Japanese ginseng) grown in Japan.

We have proposed that the life-prolonging effect of ginseng described by Shennong (7) during the Liang Dynasty in China may be due to the preventive activity of ginseng against the development of cancers. Employing a long term anticarcinogenesis model using newborn mice (8, 9), we carried out extensive experiments in 1978 to investigate whether ginseng inhibited carcinogenesis, and demonstrated that the red ginseng extracts of *Panax ginseng* C.A. Meyer cultivated in Korea had anticarcinogenic activity against lung tumors and liver cancer induced by urethane or aflatoxin B_1.

The extract was found to partly elevate natural killer cell activity (10), the results providing the hope for natural products preventing human cancers. The medium-term (9 weeks) model system also revealed anticarcinogenicity of ginseng on pulmonary adenoma induced by benzo(a)pyrene (BP) in newborn mice (11-14).

Employing BP as carcinogen, we further investigated whether fresh ginseng or white ginseng also had the similar anticarcinogenic effects, and whether the anticarcinogenic effects depended on types and ages of ginseng. We found a significant anticarcinogenic effect of 6-yr-old dried powder or fresh ginseng extract, 5- and 6-yr-old white ginseng powder or extract, and 4-, 5-, and 6-yr-old red ginseng powder or extract (15-17). The results demonstrated that the anticarcinogenicity was more prominent in aged or heat treated extract of fresh ginseng and red ginseng prepared by steaming.

In light of the above described evidences, in 1987 we began a case-control study with 905 pairs (18) to confirm whether red ginseng extracts had anticarcinogenic effect on human cancers as much as on mice, and we later extended the number of subjects to 1,987 pairs (19) from 905 pairs.

Also, a prospective study (20) was started to find whether ginseng intake was related to the type of cancers, and to evaluate the preventive effect of ginseng among the population residing in ginseng cultivation area 6 months after the first case-control study (in August 1987) and compared the results with three independent analyses in 10 yr of follow up period.

MATERIALS AND METHODS

Case-control study with 905 pairs

The cases and controls were selected from the patients admitted to the Korea Cancer Center Hospital (KCCH), Seoul. As a major cancer centre in Korea, the KCCH diagnosed average 5,000 new cancer patients annually between 1 July 1982 and 30 June 1987. These represent an average of 14% of all cancer patients diagnosed annually in 66 hospitals in Korea (21). Selection criteria for cases were: newly diagnosed cancer during the period of 1 February 1987 through 31 January 1988, diagnosis of cancer by pathological examination, and 20 yr of age or older at diagnosis. Patients admitted to the intensive care unit or the otolaryngology department were excluded from the study, because of the difficulty in answering questions. A total of 905 cases met these criteria and all cases agreed to participate in the study.

One control was selected for each case from a pool of patients diagnosed with non-cancerous diseases at the same hospital by matching gender, age at diagnosis ($\pm$2 yr), and date of admission ($\pm$3 months). When more than one control fell within the selection range, the control which had the admission date closest to that of the cancer patient was selected as the matched control. Patients whose final diagnoses were not cancer but whose diseases were associated with smoking or alcohol consumption were also excluded from the control group. Among the controls were those suffering from cardiovascular disease, chronic obstructive pulmonary disease, peptic ulcer, and liver cirrhosis.

Two trained interviewers visited the 905 case-control pairs in the hospital. To prevent possible bias between the interviewers, a standardized questionnaire was administered to each case-control pair by the same interviewer. During the interview, some information on demographic characteristics (i.e., age, marital status, education, occupation and income), life-style (i.e., cigarette smoking, alcohol consumption and others), and ginseng consumption were obtained (18).

In order to collect information on ginseng intake, a dietary-recall method commonly employed in epidemiological studies on diet and disease was used (22). In the questionnaire, ginseng types were classified into fresh ginseng, white ginseng and red ginseng. Fresh ginseng is less than four yr old and can be consumed in the fresh state. White ginseng is grown for four to six year, peeled and dried to reduce the water content to 12% or less. Red ginseng is harvested after six year, steamed, and dried. In the questionaire, each type of ginseng was further grouped into several forms of ginseng product; i.e., fresh sliced, juice, extract, powder, tea, tablet, capsule and other forms. The lifetime consumption of ginseng was assessed by asking types and products used, frequency of intake per day, week, and month for each decade of life. In addition, multiple combinations among fresh, white and red ginsengs were included.

Interviews on ginseng intake were carried out by asking the following series of questions; 1) Have you ever consumed ginseng? 2) At what age did you first take ginseng? 3) What type of ginseng products have you taken? and 4) How often (frequency) and 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). The trained interviewers obtained information by using a precoded ques-

tionnaire that took approximately half an hour to complete.

To measure the reliability of recall of ginseng use, a second interview was carried out with 180 randomly selected subjects by the same interviewer one year after the first interview, using the same questionnaire. The strength of agreement on ginseng intake information obtained from the two interviews was measured by Kappa statistic (23).

Case-control study with 1,987 pairs

In order to explore further (a) the types of ginseng products that have the most prominent cancer preventive effect, (b) the reproducibility of the dose-response relationship, (c) the duration of ginseng consumption that has a significant preventive effect, (d) the types of cancer that can be prevented by ginseng, and (e) the effect of ginseng on cancers associated with smoking, we increased the number of subjects to 1987 pairs for a case-control study (20).

All the cases were admitted to the Korea Cancer Center Hospital between February 1987 and December 1990, and were confirmed by cytological and/or histopathological examination.

The cases and controls were selected as described in the previous study (18). The disease sites of male control patients were stomach (495), thyroid (120), colon (81), kidney (93), oral cavity (85), lung (51), and others (95). For female control patients, they were uterus (351), breast (177), thyroid (170), ovary (75), stomach (46), liver (25), colon (16), and others (55). The types of diseases of the controls were mainly acute diseases; acute or unspecified gastritis, goiter, acute appendicitis, colon obstruction, acute pyelonephritis, kidney stone, tonsilitis, laryngopharyngitis, pneumonia and pleurisy. All questionnaires were checked as described in the earlier case-control study (18) of 905 pairs. To evaluate the accuracy of the answers to the questionnaire, 10% of each cases and controls were evaluated by k value (24).

Prospective study with population

The study population was selected from persons who were listed in the 1987 resident's list which was registered at the provincial government offices of the ginseng production areas. These lists contain the name, sex, date of birth, and permanent and present addresses. Subjects born before 1947 (over 40 yr) were selected. A cohort of 4,634 persons over 40 yr of age residing in Kangwha-eup was interviewed and examined between August 1987 and December 1989. Each study subject was interviewed by means of a standard questionnaire about demographic characteristics, life-long occupation, smoking and drinking habits, and past history of diseases, etc. In an attempt to obtain detailed information on ginseng intake, we used the same questionnaire as used in the previous two case-control studies (18, 19). The interviewers had been instructed and trained beforehand to ensure uniformity in the method of inquiry. We carried out follow-up studies on all cohort members to document 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 1997 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, privileged data of Korea Medical Insurance Corporation, etc.

RESULTS

905 pairs case-control study

Distribution of selected cases by cancer site for each gender is shown in Table 1. Of the 905 cases, 562 (62%) had a history of ginseng intake compared to 674 (75%) of the controls ($p<0.01$). The odds ratio (OR) for cancer in relation

Table 1. Distribution of cancer sites in 905 case subjects

Site of cancer	No. of subjects	
	Male	Female
Liver	101	13
Lung	82	29
Stomach	80	42
Larynx	14	3
Cervix	0	178
Breast	0	84
Thyroid	0	27
Others	135	92
Total	436	469

Table 2. Odds ratios and 95% confidence intervals (CI) for cancers by ginseng intake in 905 pairs

Type of ginseng	Cases	Controls	Odds ratio	95% CI*
No intake of ginseng	343	231	1.00	Reference
Intake of ginseng	562 (62%)	674 (75%)	0.56	0.46-0.69
Fresh ginseng				
Slice	103	94	0.74	0.53-1.04
Juice	39	34	0.77	0.46-1.30
Extract	13	64	0.14	0.07-0.26
White ginseng				
Powder	28	43	0.44	0.26-0.75
Extract	247	261	0.64	0.50-0.82
Tea	37	27	0.93	0.53-1.61
Red ginseng				
Extract	2	3	0.45	0.05-3.32
Combination	10	25	0.27	0.13-0.53

Adjusted for age, sex, marital status, educations, smoking, and alcohol consumption. *CI: confidence interval

Table 3. Odds ratios of cancer in ginseng intake frequency and 95 % confidence intervals in 905 pairs case-control study

Frequency of ginseng intake	Male			Female		
	Cases	Controls	Odds ratios (95% CI)	Cases	Controls	Odds ratio (95% CI)
No intake	117	56	1.00	226	175	1.00
1-3 times/yr	132	108	0.58 (0.38-0.90)	111	106	0.81 (0.57-1.15)
4-11 times/yr	104	115	0.43 (0.28-0.67)	75	103	0.56 (0.39-0.82)
Once/month or more	83	157	0.25 (0.16 - 0.39)	57	85	0.52 (0.35-0.78)
Total	436	436		469	469	
Linear trend test (1 d.f.)		45.59 (p<0.0001)			3.98 (p<0.05)	
$\times^2$ homogeneityt test (3 d.f.)		47.28 (p<0.0001)			16.53 (p<0.001)	

Table 4. Subjects response to ginseng intake questions at two different interviews

Second interview	First interview			
	None	Fresh ginseng	White ginseng	Total
None	0.57 (104)	0.05 (9)	0.01 (2)	0.63 (115)
Fresh ginseng	0.05 (8)	0.21 (39)	0.01 (1)	0.27 (48)
White ginseng	0.02 (4)	0.01 (1)	0.07 (12)	0.10 (17)
Total	0.64 (116)	0.27 (49)	0.07 (15)	1.00 (180)

Overall proportion of observed agreement

P_0=0.57+0.21+0.07=0.85

Overall proportion of chance-expected agreement

pe=0.64×0.63+0.27×0.27+0.09×0.11=0.49

Kappa value

$\frac{A}{k} = \frac{0.85-0.49}{1-0.49} = 0.71$ (p<0.01)

Table 5. Odds ratios and 95% confidence intervals for cancers by ginseng intake in 1,987 pairs

Type of ginseng	Cancer patients	Controls	Odds ratio	95% CI
No intake of ginseng	921	605	1.00	Reference
Intake of ginseng	1,066 (62%)	1,382 (75%)	0.50	0.44-0.58
Fresh ginseng				
Slice	210	172	0.79	0.63-1.01
Juice	69	63	0.71	0.49-1.03
Extract	146	255	0.37	0.29-0.46
White ginseng				
Powder	60	129	0.30	0.22-0.41
Extract	373	442	0.57	0.48-0.68
Tea	43	41	0.69	0.45-1.07
Red ginseng				
Extract	6	17	0.20	0.08-0.50
Combination	22	58	0.16	0.10-0.25

Adjusted for age, sex, marital status, educations, smoking, and alcohol consumption.

to ginseng intake was 0.56 [95% confidence interval (CI), 0.45-0.69]. Ginseng extract and powder were shown to be more effective than fresh sliced ginseng, the juice, or tea in reducing the OR (Table 2). With the increased frequency of ginseng intake, ORs decreased in both male and female (Table 3). A trend test showed a significant decrease in the number of cancer cases among those who reported an increased frequency of ginseng intake for males (p<10^{-5}) as well as for females (p<0.05). The reliability of recall for ginseng use was assessed by twice interviewing one-tenth of the randomly selected subjects using the same questionnaire. The overall agreement in reported ginseng use between the two interviews was 0.85, and the k value was 0.71 (p<0.01) (Table 4). These results strongly support the hypothesis that ginseng has cancer preventive effects, as suggested by the previous animal experiments (8-17).

1,987 pairs case-control study

In this study, as with the previous study, ginseng users had a lower risk (OR; 0.50) for cancer compared with non-users. With respect to the type of ginseng, the ORs for cancer were 0.37 for fresh ginseng extract users, 0.57 for white ginseng extract users, 0.30 for white ginseng extract users, 0.30 for white ginseng powder users, and 0.20 for red ginseng users (Table 5). Those who took fresh ginseng slices, fresh ginseng juice, and white ginseng tea, however, showed no decrease in the risk. Overall, the risk decreased as the frequency and duration of ginseng intake increased, showing a dose-response relationship (Table 6). With respect to the site of cancer, the odds ratios were 0.47 for cancer of lip, oral cavity, and pharynx; 0.20 for esophageal cancer; 0.36 for stomach cancer; 0.42 for colorectal cancer; 0.48 for liver cancer; 0.22 for pancreatic cancer; 0.18 for laryngeal cancer; 0.55 for lung cancer; 0.15 for ovarian cancer; and 0.48 for other cancers (Table 7). With cancers of the female breast, uterine cervix, urinary bladder, and thyroid gland, however, there was no benifit with ginseng intake. In cancers of lung, lip, oral cavity, pharynx, and liver, smokers who took ginseng showed decreased OR compared with smokers with no ginseng intake. These findings supported the view that the use of ginseng decreased the risk for most cancer compared to the non-user. Smokers without ginseng intake showed significantly increased risks for cancers of lung, lip, oral cavity, pharynx, and liver. However, the ORs for smokers who had consumed ginseng decreased, showing 1.99 for lung, 2.36 for lip, oral cavity, and pharynx cancers, and 2.09 for liver cancer compared with nonsmokers who had consumed ginseng. In cancers of esophagus, stomach, and colorectum, there

Table 6. Distribution of ginseng intake frequency in cases and controls by sex: Odds ratios for cancer and 95 percent confidence interval in case-control study with 1,987 pairs

Ginseng intake	Males				Females			
	Case	Controls	Odds ratio	95% CI	Cases	Controls	Odds ratio	95%
Frequency of ginseng intake								
None	409	234	1.00	Reference	512	371	1.00	Reference
1-3 times/yr	246	231	0.62	0.49-0.79	171	209	0.60	0.47-0.76
4-11 times/yr	197	223	0.48	0.37-0.62	127	171	0.54	0.42-0.71
1 time/month or more	220	384	0.31	0.25-0.39	105	164	0.47	0.39-0.62
Total lifetime consumption of ginseng								
None	409	452	1.00	Reference	512	371	1.00	Reference
1-50	452	501	0.51	0.42-0.63	322	402	0.58	0.48-0.71
51-100	75	100	0.41	0.29-0.58	28	39	0.56	0.34-0.93
101-300	80	131	0.32	0.23-0.44	29	54	0.39	0.25-0.61
301-500	20	29	0.33	0.18-0.62	8	21	0.29	0.14-0.63
500-	36	77	0.25	0.16-0.38	16	28	0.42	0.23-0.79

Table 7. Odds ratios for various cancers according to ginseng intake in case-control study with 1,987 pairs

Site of cancer	Cases	Controls	Odd ratios	95% CI
	Never taken/ever taken	Never taken/ever taken		
Lip, oral cavity, and pharynx	67/92	40/119	0.47	0.29±0.76
Esophagus	40/47	14/73	0.20	0.09±0.38
Stomach	142/158	76/224	0.36	0.09±0.52
Colon and rectum	55/63	32/86	0.42	0.24±0.74
Liver	108/156	67/197	0.48	0.33±0.70
Pancreas	12/11	5/18	0.22	0.05±0.95
Larynx	21/19	8/32	0.18	0.06±0.54
Lung	120/156	81/195	0.55	0.38±0.79
Female breast	82/92	70/109	0.63	0.40±1.05
Cervix uteri	156/146	312/170	0.72	0.52±1.01
Ovary	17/5	8/14	0.15	0.04±0.60
Urinary bladder	23/40	16/47	0.64	0.28±1.47
Thyroid gland	16/24	14/26	0.96	0.38±2.44
Other	53/61	35/79	0.48	0.27±0.85

Adjusted for age, sex, marital status, education, smoking, and alcohol consumption.

was no association with ginseng intake (Table 8).

Cohort study on population

The total number of subjects interviewed was 4,675. Out of them, 41 prevalent cancer cases were excluded, and the remaining 4,634 eligible subjects (2,362 men and 2,272 women) were selected for analysis. From 4,634 people eligible for analysis, 47 unknown diseases were excluded, and 54.7% of 137 cancer cases had history of ginseng intake in comparison with 71.2% of 4,450 non-cases, showing similar proportion to those of the control groups in the previous case-control studies [74.5% (Table 2) and 69.6% (Table 5) (18, 19)]. The present study showed a significant reduction of relative risk (RR) (0.40) by the intake of ginseng (Table 9), as shown in the previous case-control studies. On the type of ginseng, the RRs for cancer in fresh ginseng extract consumers and consumers with multiple combinations were significantly reduced (Table 9). The RRs for other types of ginseng including white ginseng tea showed a decreasing trend, but was not statistically significant. Among 24 red ginseng consumers, there were no deaths from cancer. The results showed no relationship between fresh ginseng consumers and cancer, which was consistent with the experimental study (12-17) and case-control studies (18, 19). There was a decreased risk with increased frequency of ginseng consumed, showing a significant dose-response relationship (Table 10).

During the study period, 137 cases including 42 stomach, 24 lung, 14 liver and 57 at other sites were diagnosed as cancers. The RRs in 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 a statistical significance (Table 11). Among ginseng preparations, only fresh ginseng extract consumers, a decreased risk for gastric cancer (RR=0.33, 95% CI: 0.12-0.88 was observed), while other types of ginseng

Table 8. Odds ratios for cancers according to ginseng intake and smoking in case-control study with 1,987 pairs

Cancers	Ginseng intake	Nonsmokers		Smokers	
		Odds ratio	95% CI	Odds ratio	95% CI
Lung	Ever taken	1.00 (27)*	Reference	1.99 (81)	1.25-3.19
	Never taken	2.11 (40)	1.08-4.15	4.13 (128)	1.90-9.03
Lip, oral cavity, and pharynx	Ever taken	1.00	Reference	2.36 (43)	1.23-4.51
	Never taken	2.13 (24)	0.95-4.79	4.41 (69)	1.29-15.04
Esophagus	Ever taken	1.00 (5)	Reference	0.13 (35)	0.06-0.31
	Never taken	0.51 (5)	0.10-2.69	0.38 (42)	0.09-1.62
Stomach	Ever taken	1.00	Reference	2.90 (62)	1.79-4.70
	Never taken	2.73 (80)	1.61-4.64	1.90 (101)	0.84-4.28
Colorectum	Ever taken	1.00 (31)	Reference	3.25 (20)	1.25-8.44
	Never taken	2.11 (35)	1.03-4.34	2.45 (31)	0.60-10.13
Liver	Ever taken	1.00 (31)	Reference	2.09 (81)	1.33-3.29
	Never taken	1.68 (27)	0.79-3.57	2.50 (125)	1.06-5.92

Adjusted for age, sex, education, and alcohol consumption. *: Odds ratio (No. of patients)

Table 9. Relative risks for cancer by ginseng intake in cohort study

Ginseng intake	No. of subjects	No. of cancer cases	Relative risk	95% CI
No intake	1,283	62	1.00	–
Ginseng intake	3,167	75	0.40*	0.28-0.56
Slices & juice	236	8	0.67	0.33-1.32
Extract	296	3	0.31*	0.13-0.74
White ginseng				
Powder	147	5	0.49	0.19-1.23
Extract	68	1	0.50	0.12-2.07
Tea	442	18	0.65	0.37-1.12
Red ginseng				
Extract	24	–	–	–
Boiled chicken with young ginseng root	381	12	0.71	0.38-1.21
Multiple combination	1,573	28	0.34*	0.20-0.53

Relative risks, adjusted for age, sex, education, smoking and alcohol consumption; *: $p<0.05$

Table 10. Relative risks for cancer according to frequency of ginseng intake in cohort study

Frequency of ginseng intake	Relative risk			
	No. of no-cancers	No. of cancers	risk	95% CI
No intake	1,283	62	1.00	–
1-3 times/yr	1,439	39	0.46	0.30-0.69
4-11 times/yr	924	21	0.35	0.21-0.58
Once/month or more	804	15	0.34	0.20-0.59

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

showed a decreasing trend.

DISCUSSION

In China, red ginseng was found to inhibit development of diethylnitrosamine-induced liver cancer in rats (25) and skin cancer in mice (26). In Russia, tissue-culture biomass tincture obtained from cultured *Panax ginseng* cells was shown to have a strong inhibitory effect on rat mammary adenocarcinoma induced by methyl-N-nitrosourea (27) as well as development of experimental uterine cervix and vaginal tumors (28). The result that 12-*o*-tetradecanoylphorbol-13-acetate (TPA)-induced production of tumor necrosis factor in mouse skin was inhibited by methanol extract of heat-processed neoginseng pretreatment was obtained in Korea (29). Recently, Japanese workers observed that, dietary administration of red ginseng powder during the initiation stage of carcinogenesis suppressed preneoplastic lesions in the colon of rats induced by 1,2-dimethylhydrazine (30). In MCF-7 breast cancer cells, the ability of American ginseng to induce the oestrogen-regulated gene *pS2* and to regulate the cell-cycle were assessed in the U.S.A. Both American ginseng and oestradiol equally induced *pS2* RNA expression, but only the ginseng caused a dose-dependent decrease in cell proliferation (31).

In case-control studies with 905 pairs and 1,987 pairs, there was noticeable decrease in risk by intake of ginseng extract compared to intake of fresh ginseng and there was a dose-response relationship depending on frequency of ginseng intake. The ORs of ginseng consumers decreased in all kinds of cancers. These results strongly support the hypothesis that ginseng has cancer preventive effects, as suggested by the earlier animal experiments. Lancet stated in an editorial that our study was one example of needed research into non-organ specific strategies for cancer control (32). Furthermore, the results of the cohort study also suggest that *Panax ginseng* C.A. Meyer has non-organ specific preventive effect against cancer, providing support for the previous case-control studies.

By comparing experimental results of types and ages of ginseng including two case-control and one cohort studies, the result with less than 5 yr-fresh ginseng was negative in both experimental and epidemiological studies but positive

Table 11. Adjusted relative risks for selected cancers by ginseng intake in cohort study

Ginseng intake	No. of subjects	Cancers (n)								
		Stomach (42)			Lung (24)			Liver (14)		
		No.	RR	95% CI	No.	RR	95% CI	No.	RR	95% CI
No intake	1,283	23	1.00	–	14	1.00	–	4	1.00	–
Ginseng intake	3,167	19	0.33*	0.18-0.57	10	0.30*	0.14-0.65	10	0.86	0.25-2.94
Slices & 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	0.15-4.87
Red ginseng										
Extract										
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

RR: Relative risks, adjusted for age, sex, education, smoking and alcohol consumption; *: $p<0.05$; CI: Confidence interval; Value in parentheses indicate number of cancer cases.

Table 12. Comparison of relative risks for cancer by type of ginseng intake by medium-term experiment, case-control studies and cohort study

Kind of ginseng	Anticarcinogenicity confirmed by Yun's test model	Case-control studies		Cohort study based on population
		905 pairs Relative risks	1,987 pairs Relative risks	4,634 persons/5 yr Odds ratios
Ginseng intake		0.56*	0.50*	0.40*
Fresh ginseng				
Fresh slices	1.5, 3, 4 and 5 yr-old 6 yr-old only *	0.74	0.79	0.67
Extract	1.5, 3, 4 and 5 yr-old 6 yr-old only *	0.14*	0.37*	0.31*
White ginseng				
Powder	1.5, 3 and 4 yr-old 5 and 6 yr-old*	0.44*	0.30*	0.49
Extract	1.5, 3 and 4 yr-old 5 and 6 yr-old*	0.64*	0.57*	0.50
Red ginseng				
Extract	1.5 and 3 yr-old 4,5 and 6 yr-old*	0.45	0.20*	24 participants = No cancer death =
Powder	1.5 and 3 yr-old 4,5 and 6 yr-old*			
Combination	–	0.27*	0.16*	0.34*

Adjusted for age, sex, education, smoking, alcohol consumption; *: Statistically significant.

in fresh ginseng extract (Table 12). On the other hand, there was no cancer death among 24 red ginseng consumers, and red ginseng products showed prominent preventive effect in the 9 week anticarcinogenicity test model (Yun's model) and both case-control and cohort studies.

In order to compare the dose-response relationship between ginseng consumption and trend test of the above described results showed a significant decrease in proportion of cancer cases with increasing frequency of intake for both males and females (Table 13).

Experimental studies on ginseng has been widely carried out in many countries including Korea, China, Japan and Russia. The results indicated ginseng as an agent for anticarcinogenicity as well as antipromoter. However, epidemiological studies were published only by our groups, including two case-control and one cohort studies.

In these three epidemiological studies, we demonstrated that *Panax ginseng* C.A. Meyer decreased the risks for most types of human cancers with dose response relationship, that is, non-organ specific cancer preventive effects (32-35). The need for clinical studies of ginseng has been strongly recommended (36-40). Clinical trials of *Panax ginseng* extracts and its active compounds are now warranted to be tested for a question of whether "Can this herb prevent all kinds of cancer?"

Table 13. Comparison of dose response relationship with frequency of ginseng intake in two case-control studies and three cohort analysis

Frequency of ginseng intake	Relative risks for cancer					
	Case-control studies			Cohort analysis (4,634 Participants)		
	905 Pairs		1,987 Pairs	5 yr	7 yr	10 yr
	Male	Female	Both sex	Both sex	Both sex	Both sex
No intake	1.00	1.00	1.00	1.00	1.00	1.00
1-3 times/yr	0.58	0.81	0.60	0.46	0.29	0.52
4-11 times/yr	0.43	0.56	0.51	0.35	0.51	0.44
1 time/month <	0.25	0.52	0.36	0.34	0.34	0.47

RR adjusted for age, sex, education, smoking, alcohol consumption.

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Epidemiological study on cancer prevention by ginseng: are all kinds of cancers preventable by ginseng? J Korean Med Sci. 2001 Dec;16 Suppl(Suppl):S19-27. doi: 10.3346/jkms.2001.16.S.S19.Â Among 24 red ginseng intakers, no cancer death occurred during the follow-up period. The risk for stomach and lung cancers was significantly reduced by ginseng intake, showing a statistically significant dose-response relationship in each follow-up year. In conclusion, Panax ginseng C.A. Meyer has been established as non-organ specific cancer preventive, having dose response relationship. These results warrant that ginseng extracts and its synthetic derivatives should be examined for their preventive effect on various types of human cancers. Although red ginseng was used in the study, it is the same as white ginseng and refers to a different method of ginseng preparation. A mixture of ginseng and Chinese herbs was shown in a double-blind, placebo-controlled trial of coronary artery disease patients to improve cardiac index and stroke volume index.Â Panax ginseng has been traditionally used for the prevention and treatment of various chronic diseases and infections. The root of Panax ginseng has been a well-known and extensively used traditional medicine in East Asian countries (Korea and China) for thousands of years.Â However, there have been relatively few studies on the effect of ginseng supplementation on gastrointestinal disorders. Large bowel cancer includes cancerous growths in the colon, rectum and appendix. 98% of all cancers in the large intestine are adenocarcinomas. Several studies suggested that the use of aspirin and other NSAIDs have a protective effect against colon cancer.Â Epidemiological studies have demonstrated that dietary factors play a critical role in the development of human colon cancers [20]. Takamitsu et.al., investigated the modifying effect of dietary Peucedanum japonicum and antioxidant effect on azoxymethane (AOM)-induced rat colon carcinogenesis. Modification of the preneoplastic lesions of both aberrant crypt foci (ACF) and b-catenin accumulated crypts (BCAC) in colon carcinogenesis, microscopically and immunohistochemically was observed and it was. Centers for Disease Control and Prevention Epidemiology and Prevention of Vaccine-Preventable Diseases, 13th Edition. Meningococcal Disease. Neisseria meningitidis â—â— Severe acute bacterial.Â The incidence of serogroups C and Y, which represent the majority of cases of meningococcal disease preventable by the conjugate vaccines, are at historic lows. However, a peak in disease incidence among adolescents and young adults 16 to 21 years of age has persisted, even after routine vaccination of adolescents was recommended in 2005.