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Original Article

Association Between Ginseng Intake and Mortality: Kangwha Cohort Study

Sang-Wook Yi, M.D., Ph.D.,[1] Jae Woong Sull, Ph.D.,[2,3] Jae Seok Hong, Ph.D.,[4] John Alderman Linton, M.D.,[5] and Heechoul Ohrr, M.D., Ph.D.[2,3]

Abstract

Objective: *Panax ginseng* C.A. Meyer is a well-known medicinal herb in North America and Europe. The purpose of this study was to investigate the association between ginseng intake and mortality among members of the Korean population.
Methods: We followed 6282 subjects who were 55 years of age or older in March 1985 until December 31, 2003. The Cox proportional hazard regression model was used to evaluate effects of ginseng intake on mortality.
Results: Adjusting for age, education, occupation, drinking, smoking, self-reported chronic disease, body mass index, and blood pressure, all-cause mortality for male ginseng users was significantly lower than that for male nonusers (Hazard ratio [HR] = 0.90; 95% confidence interval [CI], 0.81–0.99). However, such an association was not observed in women (HR = 1.03; 95% CI, 0.94–1.13). Cancer-specific mortality was lower in female ginseng users than female nonusers after adjustment of relevant covariates (HR = 0.80; 95% CI, 0.60–1.08). Compared to nonusers, the HR for cancer-specific mortality in women was 0.84 in infrequent users (95% CI, 0.62–1.15) and 0.61 in frequent users (95% CI, 0.32–1.14) (p for trend, 0.09), which is not statistically significant. The cancer-specific mortality was not associated with ginseng intake in male subjects (HR = 0.95; 95% CI, 0.76–1.20). Mortality caused by cardiovascular diseases was not related to ginseng intake in both men and women.
Conclusion: The 18.8-year progressive cohort study showed that ginseng intake decreased all-cause mortality in older males, but such life prolongation effect was not shown in women.

Introduction

Ginseng, a deciduous perennial plant, has been proposed as a medicinal herb to enhance stamina and cure many diseases in Asia, especially Korea and China, for thousands of years.[1] In the western world, ginseng has been sold in various types of food supplement at health food stores, drugstores, and superstores.[2] Ginseng has been among the top ten selling herbal supplements in the United States over the past decade.[3]

Among 13 species of ginseng known so far,[1] *Panax ginseng* C.A. Meyer (Korean ginseng) and *P. quinquefolium* L. (American ginseng) are highly valued and most utilized across the world. Modern therapeutic claims for *P. ginseng* refer to vitality, immune function, cancer, cardiovascular disease, cognitive and physical performance, and sexual function.[4] The efficacy of ginseng has been studied largely through animal testing and experimental research,[5] but studies based on randomized clinical trials or population observation are rare.

With regard to population studies on ginseng, two case-control studies[6,7] and three cohort studies have been reported so far.[8–10] Like most *in vivo* animal studies and *in vitro* experimental studies, these population studies examined mainly the preventive or therapeutic effect of ginseng against cancer. Although its effect on prolongation of life was described in *Shen Nong Ben Cao Jing* (The Divine Farmer's Materia Medica), one of the oldest pharmacopoeias in the world,[11] any association of ginseng intake with mortality among the general population of a local community has not been previously reported.

This study examined the relationship between ginseng intake and mortality from all causes, cancers, and cardiovascular diseases through a long-term prospective cohort study in Kangwha county, one of famous ginseng cultivating lands in Korea.

[1]Department of Preventive Medicine and Public Health, Kwandong University College of Medicine, Gangneung, Republic of Korea.
[2]Institute for Health Promotion, [3]Department of Epidemiology and Health Promotion, Graduate School of Public Health, Yonsei University, Seoul, Republic of Korea.
[4]Health Insurance Review Agency, Seoul, Republic of Korea.
[5]Department of Family Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea.

Methods

Study population and location

This study used the data of the Kangwha Cohort Study.[12,13] Among 9378 residents of Kangwha county who were 55 years or older in February 1985, 6372 subjects (67.9%) participated in interviews about ginseng use, and measurements of blood pressure and body mass. Those who had no information on ginseng intake ($n = 51$) at entry or was not followed up after the initial survey ($n = 39$) were excluded, and thus the final study population recruited was 6282 (male, 2695; female, 3587). Kangwha county consists of several islands approximately 50 km west from Seoul. Its population was 71,116 in 1993[14] and it had one of the areas of cultivation of *P. ginseng* C.A. Meyer in Korea.[8]

Baseline data collection and follow-up

The initial survey for the Kangwha Cohort Study was conducted over a month in March 1985. Each subject was interviewed using a structured questionnaire to collect data on demographic characteristics: education, occupation, health conditions at entry, health behaviors, diet, and other factors. Blood pressure, height, and weight were measured by trained investigators. For the question "How often do you take ginseng, including ginseng liquor (any amount)?," participants were asked to choose from "very often, often, occasionally, never." The study subjects were followed up until December 31, 2003, and thus the maximum period of follow-up for death was 18.8 years. The total observed person-times was 30,505 person-years.

Outcome assessment

The outcomes of this study are all-cause deaths and cause-specific deaths. Data on deaths and their causes from January 1, 1992 to December 31, 2003 were obtained from the Statistics on the Causes of Death of Korea of the Korea National Statistical Office. The data from March 1985 to December 31, 1991 were collected either through calls and visits of trained surveyors twice a year or from records of burial and death certificates of *eup* and *myeon* offices (administrative branch offices of local government in Korea). The International Classification of Diseases 10th Revision (ICD-10) was applied to define the causes of death, which were classified into cancers (C00-C99) or total cardiovascular diseases (I00-I99).

Statistical analysis

Ginseng users were grouped into infrequent users (occasionally) and frequent users (very often, often) to examine the relationship between ginseng intake and mortality more closely. Sociodemographic characteristics and potential variable factors for infrequent users and frequent users were controlled with ANOVA and Chi-square test. HR and 95% CI, survival function, and hazard function for ginseng intake were calculated with the Cox proportional hazard regression model. The variables adjusted in our study were: age at entry (years); education (none, elementary school, middle school, or higher); occupation (agriculture, other); drinking (current drinker, non-drinker); smoking (current smoker, past smoker, never); self-reported chronic disease at entry (yes, no); body mass index (< 25, $= 25$); and elevated blood pressure (systolic blood pressure (SBP) = 140 or diastolic blood pressure (DBP) = 90, SBP < 140 and DBP < 90). All analyses were made by sex separately (Table 1).

Since users who had a disease or health problem at entry might take ginseng or there would be a lag time until ginseng took effect for subjects starting ginseng intake around study entry, we also implemented a lag time analysis in which those whose follow-up ended before December 31, 1989 (with less than 4.8 years of follow-up) were excluded from analysis. In the trend test, nonusers were numbered as 1, infrequent users as 2, and frequent users as 3, and ginseng intake was set as a continuous variable. We estimated the survival function and risk function of mortality against ginseng intake with adjustment for all variables using the Cox proportional hazard regression model, and examined how differently ginseng intake took effect for each follow-up period.[15] HR, 95% CI, and p-values in this study were all calculated by the two-tail test. The SAS System for Windows v. 9.13 was used for statistical analysis.

Results

Sixty-nine percent of males (1848/2695) and 51% of females (1832/3587) were ginseng users (infrequent or frequent users). The crude all-cause mortality rate of nonusers, infrequent, and frequent users was 72.7, 61.6, and 56.3 deaths/1000 person-years in men; and 42.7, 38.1, and 38.9 deaths/1000 person-years in women, respectively. Male ginseng users were younger, more educated, and drank more than nonusers; male infrequent users smoked more and were more hypertensive than male nonusers or male frequent users. Female ginseng users were younger, more educated, but had less alcohol consumption than nonusers; and female frequent users smoked more but were less hypertensive than the other two female groups.

Unadjusted HR showed that ginseng intake was significantly associated with decreasing all-cause mortality in both men (HR=0.81; 95% CI, 0.74–0.89) and women (HR=0.89; 95% CI, 0.81–0.97). After adjustment for age and other variables, ginseng intake was still significantly associated with all-cause mortality in men. And the analysis using 4.8 years lag time for male groups produced the statistically significant result of more decreased death risk (HR = 0.82) than when no lag time was applied. But such associations were not observed in women (Table 2).

Survival function estimates for all-cause mortality were adjusted for all variables using the Cox proportional hazards model. Male ginseng users showed a noticeably higher survival rate pattern than male nonusers from around year 5 (Fig. 1), whereas the survival rate of female ginseng users was higher than that of female nonusers from years 1 to 14, with the gap narrowing thereafter (Fig. 2). On the hazard function curve, all-cause mortality risk of male ginseng users is lower than male nonusers from around year 5 (mean monthly hazard function for users vs. nonusers: follow-up $<$ 60 months, 0.0036 vs. 0.0038; follow-up $\geqq$ 60 months, 0.0064 vs. 0.0084), but all-cause mortality risk of female ginseng users is higher than that of female nonusers from around year 14–15 (mean monthly hazard function for users vs. nonusers: follow-up $<$ 168 months, 0.0023 vs. 0.0029; follow-up = 168 months, 0.0064 vs. 0.0058).

TABLE 1. BASELINE CHARACTERISTICS ACCORDING TO GINSENG INTAKE BY SEX IN KANGWHA COHORT STUDY, 1985–2003

	Men				*Women*			
	Ginseng intake				*Ginseng intake*			
	Nonuser	*Infrequent user*	*Frequent user*	p	*Nonuser*	*Infrequent user*	*Frequent user*	p
Number of subjects	847	1312	536		1755	1528	304	
Total observed person-years	8,939	15,114	6453		23,263	21,410	4321	
Number of deaths	650	931	363		994	816	168	
Crude death rate (deaths/1000 person-years)	72.7	61.6	56.3		42.7	38.1	38.9	
Observed person-years	10.6 ± 6.4	11.5 ± 6.5	12.0 ± 6.3	<0.001	13.3 ± 6.3	14.0 ± 6.0	14.2 ± 5.7	<0.001
Age at entry	67.5 (7.8%)	66.0 (6.9%)	65.4 (6.9%)	<0.001	67.9 (9.0%)	66.3 (8.1)	66.1 (7.9%)	<0.001
Body mass index	21.6 (2.7%)	21.8 (2.6%)	21.8 (2.7%)	0.15	22.7 (3.2%)	22.5 (3.3)	22.7 (3.3%)	0.22
Education								
No education	399 (47%)	530 (40%)	160 (30%)	<0.001	1489 (85%)	1194 (78%)	211 (69%)	<0.001
Elementary school	391 (46%)	683 (52%)	311 (58%)		255 (15%)	313 (20%)	81 (27%)	
Middle School or over	56 (7%)	99 (8%)	65 (12%)		10 (1%)	21 (1%)	12 (4%)	
Occupation								
Agriculture	720 (85%)	1159 (88%)	423 (79%)	<0.001	1398 (80%)	1254 (82%)	228 (75%)	0.01
Other	126 (15%)	153 (12%)	113 (21%)		356 (20%)	274 (18%)	76 (25%)	
Smoking								
Current smoker	608 (72%)	1001 (76%)	392 (73%)	0.05	388 (22%)	331 (22%)	85 (28%)	0.01
Never smoker	176 (21%)	224 (17%)	94 (18%)		1316 (75%)	1174 (77%)	214 (70%)	
Past smoker	63 (7%)	87 (7%)	50 (9%)		51 (3%)	23 (2%)	5 (2%)	
Drinking								
Non-drinker	325 (38%)	437 (33%)	180 (34%)	0.04	1560 (89%)	1398 (91%)	268 (88%)	0.03
Current drinker	522 (62%)	873 (67%)	356 (66%)		195 (11%)	130 (9%)	36 (12%)	
Elevated blood pressure								
No	367 (44%)	494 (38%)	224 (42%)	0.02	711 (41%)	626 (41%)	132 (44%)	0.61
Yes[a]	475 (56%)	811 (62%)	309 (58%)		1032 (59%)	891 (59%)	169 (56%)	
Chronic disease								
Never	454 (54%)	739 (56%)	273 (51%)	0.09	886 (50%)	745 (49%)	146 (48%)	0.53
Ever	393 (46%)	573 (44%)	263 (49%)		869 (50%)	783 (51%)	158 (52%)	

[a]Systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90.

Table 2. Association of Ginseng Intake with All Causes of Death and Deaths Caused by Cancers, Cardiovascular Diseases, and Unclassified Diseases in Kangwha Cohort Study, 1985–2003

	Males					*Females*				
	Nonusers		*Users*			*Nonusers*		*Users*		
	Deaths	*HR*	*Deaths*	*HR*	*95% CI*	*Deaths*	*HR*	*Deaths*	*HR*	*95% CI*
All causes of death (ICD10: A00-Z99)										
Age adjusted	650	1.0	1294	0.90	0.82–0.99	994	1.0	984	1.04	0.95–1.13
Multivariate adjusted[a]	644	1.0	1286	0.89	0.81–0.98	993	1.0	984	1.04	0.95–1.14
Multivariate adjusted[b]	624	1.0	1265	0.90	0.81–0.99	956	1.0	955	1.03	0.94–1.13
Multivariate adjusted with 4.8-year lag time[b,c]	438	1.0	884	0.82	0.73–0.92	723	1.0	758	1.05	0.95–1.17
Cancers (ICD10: C00-C99)										
Age adjusted	114	1.0	256	0.93	0.74–1.16	96	1.0	87	0.81	0.61–1.08
Multivariate adjusted[a]	113	1.0	254	0.96	0.77–1.20	96	1.0	87	0.82	0.61–1.10
Multivariate adjusted[b]	111	1.0	252	0.95	0.76–1.20	95	1.0	85	0.80	0.60–1.08
Multivariate adjusted with 4.8-year lag time[b,c]	82	1.0	171	0.82	0.63–1.07	68	1.0	67	0.85	0.61–1.20
Cardiovascular diseases (ICD 10: I00-I99)										
Age adjusted	120	1.0	281	1.03	0.83–1.28	234	1.0	237	0.99	0.82–1.18
Multivariate adjusted[a]	117	1.0	279	0.98	0.78–1.22	234	1.0	237	0.99	0.82–1.19
Multivariate adjusted[b]	110	1.0	276	1.01	0.81–1.26	229	1.0	232	0.98	0.81–1.18
Multivariate adjusted with 4.8-year lag time[b,c]	76	1.0	214	1.06	0.81–1.39	202	1.0	198	0.93	0.76–1.14

[a]For males, adjusted for age at entry (years); education (none, elementary school, middle school, higher); occupation (agriculture, other); drinking (current drinker, non-drinker); and elevated blood pressure (SBP $\geq$ 140 or DBP $\geq$ 90, SBP $<$ 140 and DBP $<$ 90). For females; adjusted for age at entry (years); education (none, elementary school, middle school, higher); occupation (agriculture, other); drinking (current drinker, non-drinker); and smoking (current smoker, past smoker, never).

[b]Adjusted for age at entry, education, occupation, drinking, smoking, chronic disease at entry (ever, never), body mass index (BMI $<$ 25.0, BMI $\geq$ 25), and elevated blood pressure (SBP $\geq$ 140 or DBP $\geq$ 90, SBP $<$ 140 and DBP $<$ 90).

[c]Analysis was done excluding subjects who had been followed-up by December 31, 1989 (less than 4.8 years follow-up).

HR, hazard ratio; CI, confidence interval.

When male cause of death was analyzed, unadjusted hazard ratio showed that ginseng intake was not associated with deaths from cancers (HR = 0.91; 95% CI, 0.73–1.14) and cardiovascular diseases (HR = 0.95; 95% CI, 0.77–1.17). After adjusting for age and other variables, male deaths caused by cancers and cardiovascular diseases had no association with ginseng intake. The exclusion of deaths during the first 4.8 years insignificantly lowered the hazard ratio of cancer mortality from 0.95 to 0.82.

In women, the unadjusted mortality risk of ginseng users was insignificantly lower for cancer deaths (HR = 0.81; 95% CI, 0.61–1.09) and cardiovascular disease deaths (HR = 0.90; 95% CI, 0.75–1.08) than that of nonusers. After adjustment for variables for female groups, however, the risk of deaths from cancers and cardiovascular diseases had no association with ginseng intake.

When the frequency of ginseng intake was taken into account for men, unadjusted all-cause mortality risk trended lower for infrequent users (HR = 0.83; 95% CI, 0.76–0.92) than for frequent users (HR = 0.76– 95%; CI, 0.67–0.87) (p for trend $<$ 0.001). In women, all-cause death risk was significantly low in infrequent users (HR = 0.89; 95% CI, 0.81–0.97) but insignificantly low in frequent users (HR = 0.90; 95% CI, 0.77–1.06) (p for trend = 0.02).

After adjusting for age and other potential variables for men, the hazard ratio was 0.90 for infrequent users and 0.87 for frequent users. With the initial 4.8 years of death excluded, the hazard ratio of infrequent users was 0.80 (95% CI, 0.71–0.91), but frequent users did not show a notable difference. The test for trends showed the risk of male all-cause mortality decreased significantly with the increasing frequency of ginseng intake regardless of adjustment for variables (Table 3). In women, after adjustment for variables, the frequency of ginseng intake had no association with all-cause mortality.

When the frequency of ginseng intake was further analyzed by cause of death for male subjects, deaths caused by cancers and cardiovascular diseases showed no association with ginseng intake frequency regardless of adjustment for variables. In the same analysis for female subjects, the unadjusted hazard ratio of cancers was 0.85 in infrequent users (95% CI, 0.63–1.15) and 0.61 in frequent users (95% CI, 0.33–1.14), indicating ginseng intake frequency proportionally lowered mortality risk with a borderline significance (p for trend $<$ 0.09). This trend remained in effect in variables-adjusted models (p for trend = 0.09). Cardiovascular disease mortality had no association with ginseng intake frequency regardless of adjustment for variables.

Discussion

From this 18.8-year population-based cohort study, we observed that ginseng intake correlated with significantly reduced all-cause mortality risk of elderly males. After adjustment for age and other variables, ginseng intake also showed a weakened but significant correlation with decreased mortality risk. The trend test showed that all-cause mortality risk decreased as ginseng intake was increased. El-

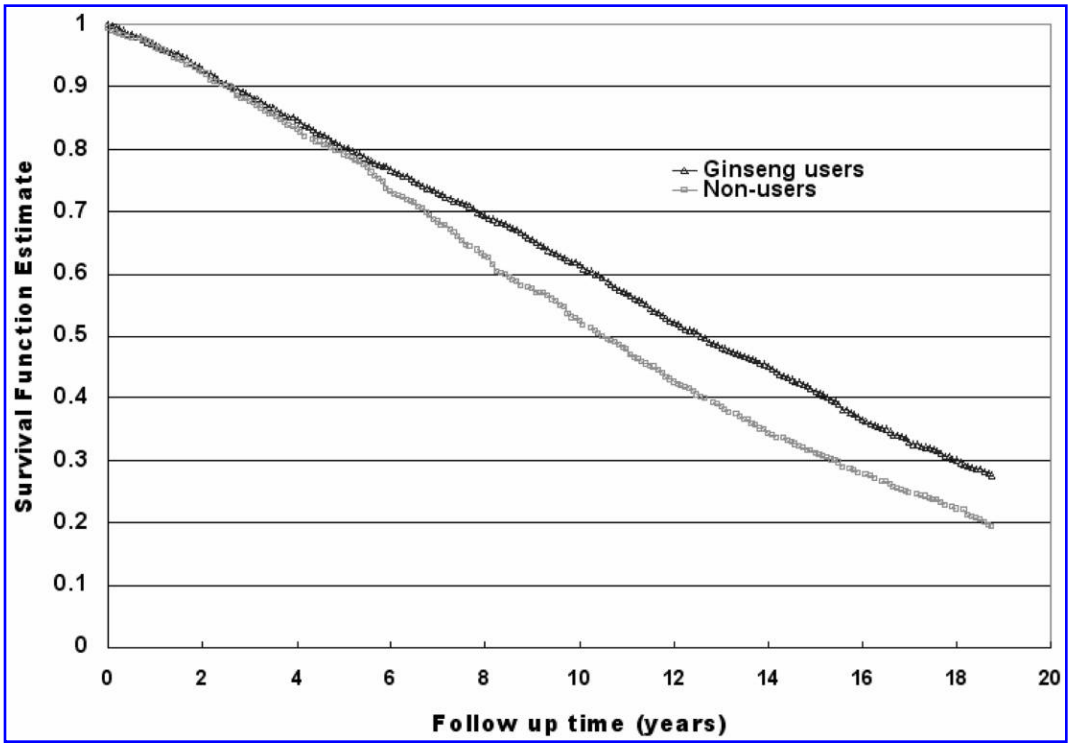

FIG. 1. Survival function estimates curve for all causes of mortality by ginseng intake among males, Kangwha Cohort Study, 1985–2003.

derly females also showed a significant association between ginseng intake and decreased mortality risk before adjustment for age and variables, but no association was shown after adjustment.

In our analysis by cause of death, ginseng intake was not significantly associated with deaths due to cancers in men or women. But it lowered the risk of mortality from cancers in women, with a relationship between greater ginseng in-

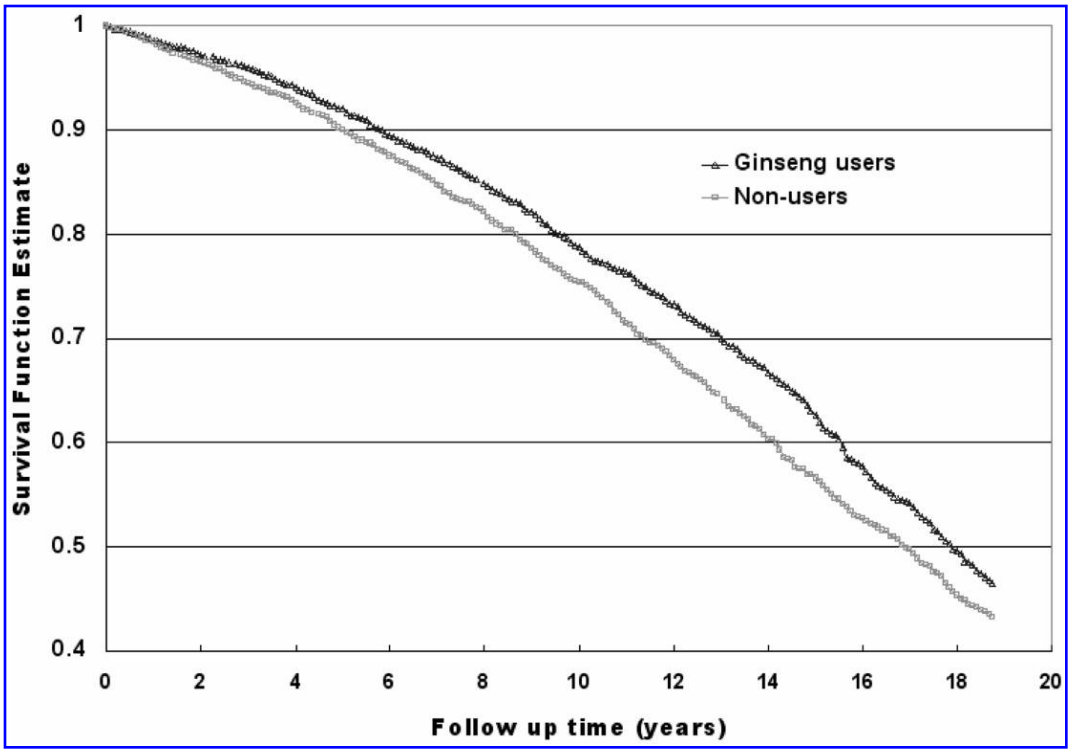

FIG. 2. Survival function estimates curve for all causes of mortality by ginseng intake among females, Kangwha Cohort Study, 1985–2003.

Table 3. Association of Ginseng Intake Frequency with All Causes of Death and Deaths Caused by Cancers, Cardiovascular Diseases, and Unclassified Diseases in Kangwha Cohort Study, 1985–2003

	Nonusers		*Infrequent users*			*Frequent users*			
	Deaths	*HR*	*Deaths*	*HR*	*95% CI*	*Deaths*	*HR*	*95% CI*	P *for trend*[d]
Males									
All causes of death (ICD10: A00-Z99)									
Age adjusted	650	1.0	931	0.91	0.82–1.01	363	0.87	0.76–0.99	0.025
Multivariate adjusted[a]	644	1.0	926	0.90	0.82–1.00	360	0.87	0.77–1.00	0.027
Multivariate adjusted[b]	624	1.0	911	0.90	0.82–1.00	354	0.87	0.76–1.00	0.030
Multivariate adjusted with 4.8-year lag time[b,c]	438	1.0	619	0.80	0.71–0.91	265	0.87	0.74–1.01	0.028
Cancers (ICD10: C00-C99)									
Age adjusted	114	1.0	178	0.92	0.72–1.16	78	0.95	0.71–1.26	0.657
Multivariate adjusted[a]	113	1.0	177	0.95	0.75–1.20	77	1.00	0.75–1.34	0.955
Multivariate adjusted[b]	111	1.0	175	0.94	0.74–1.19	77	1.00	0.74–1.35	0.941
Multivariate adjusted with 4.8-year lag time[b,c]	82	1.0	119	0.81	0.61–1.07	52	0.84	0.59–1.20	0.279
Cardiovascular diseases (ICD 10: I00-I99)									
Age adjusted	120	1.0	202	1.04	0.83–1.31	79	0.99	0.75–1.32	0.982
Multivariate adjusted[a]	117	1.0	200	0.99	0.79–1.25	79	0.93	0.70–1.25	0.656
Multivariate adjusted[b]	110	1.0	197	1.02	0.81–1.30	79	0.97	0.72–1.31	0.882
Multivariate adjusted with 4.8-year lag time[b,c]	76	1.0	148	1.04	0.78–1.37	66	1.12	0.80–1.57	0.508
Women									
All causes of death (ICD10: A00-R99, V01-Y89)									
Age adjusted	994	1.0	816	1.03	0.94–1.13	168	1.06	0.90–1.25	0.403
Multivariate adjusted[a]	993	1.0	816	1.04	0.94–1.14	168	1.07	0.90–1.26	0.339
Multivariate adjusted[b]	956	1.0	794	1.03	0.94–1.13	161	1.03	0.87–1.22	0.524
Multivariate adjusted with 4.8-year lag time[b,c]	723	1.0	624	1.04	0.94–1.16	134	1.10	0.92–1.33	0.260
Cancers (ICD10: C00-C99)									
Age adjusted	96	1.0	76	0.85	0.63–1.15	11	0.61	0.33–1.14	0.090
Multivariate adjusted[a]	96	1.0	76	0.86	0.63–1.16	11	0.63	0.34–1.18	0.113
Multivariate adjusted[b]	95	1.0	74	0.84	0.62–1.15	11	0.61	0.32–1.14	0.085
Multivariate adjusted with 4.8-year lag time[b,c]	68	1.0	59	0.91	0.64–1.29	8	0.58	0.28–1.21	0.188
Cardiovascular diseases (ICD 10: I00-I99)									
Age adjusted	234	1.0	197	0.98	0.81–1.19	40	1.00	0.71–1.40	0.919
Multivariate adjusted[a]	234	1.0	197	0.99	0.81–1.19	40	1.01	0.72–1.42	0.983
Multivariate adjusted[b]	229	1.0	192	0.97	0.80–1.18	40	1.01	0.72–1.42	0.919
Multivariate adjusted with 4.8-year lag time[b,c]	202	1.0	159	0.90	0.73–1.11	39	1.09	0.77–1.54	0.389

[a]For males, adjusted for age at entry (years); education (none, elementary school, middle school, higher); occupation (agriculture, other); drinking (current drinker, non-drinker); and elevated blood pressure (SBP $\geq$ 140 or DBP $\geq$ 90, SBP $<$ 140 and DBP $<$ 90). For females; adjusted for age at entry (years); education (none, elementary school, middle school, higher); occupation (agriculture, other); drinking (current drinker, non-drinker); and smoking (current smoker, past smoker, never).

[b]Adjusted for age at entry, education, occupation, drinking, smoking, chronic disease at entry (ever, never), body mass index (BMI $<$ 25.0, BMI $\geq$ 25), and elevated blood pressure (SBP $\geq$ 140 or DBP $\geq$ 90, SBP $<$ 140 and DBP $<$ 90).

[c]Analysis was done excluding subjects who had been followed-up by December 31, 1989 (less than 4.8 years follow-up).

[d]The trend test was done using nonuser, infrequent user, and frequent user as continuous variables 1, 2, and 3, respectively.

HR, hazard ratio; CI, confidence interval.

take and lower risk approaching significance. An earlier case-control study[6,7] and cohort study[8] by Yun and Choi reported ginseng intake had a strong preventive effect on various human cancers. It is not evident why these two former studies and this study, both on Koreans, reported differing results. Since the control group in the case-control study by Yun and Choi consisted of patients who had been admitted to the same hospital as cancer patients, their ginseng intake might have been higher than that of the general population.[10] And the study group in their cohort study was a mean 12 years younger than in this study, which can be another possible cause of difference. But when we analyzed subjects by stratified age, the effect of ginseng intake was not more evident at younger ages. For ginseng users under 65 years of age the adjusted hazard ratio of all-cause mortality was 0.95 (95% CI, 0.70–1.30) in men and 0.80 (95% CI, 0.54–1.18) in women, whereas for ginseng users 65 years of age or older it was 0.98 (95% CI, 0.70–1.36) in men and 0.76 (95% CI, 0.48–1.20) in women.

Studies in Chinese populations have reported different re-

sults on the preventive and treatment effect of ginseng intake. In the Shanghai Breast Cancer Study[9] the mortality rate of ginseng users among breast cancer patients was significantly low, whereas the Shanghai Women's Health Study[10] reported no association between ginseng intake and stomach cancer risks. Based on the varied results of studies on ginseng intake so far, the effect of ginseng as a non-organ–specific cancer preventive herbal medicine, suggested by Yun and Choi, cannot be confirmed and further research is required to examine the preventive effect of ginseng on cancer.[1,6–8, 23]

This study supports previous studies that found no relationship between ginseng intake and cardiovascular disease risk. A recent systematic review on human clinical trials for ginseng intake and cardiovascular disease risk factors reported there was no evidence that ginseng intake plays a positive role in blood pressure, glucose, and lipid profiles.[21] In our study, male ginseng users were more hypertensive than male nonusers, and after adjustment for age, sex, education, and BMI, the systolic pressure of male ginseng users was 3.3 mm Hg higher than that of male nonusers (p = 0.006). Our analysis of ginseng intake and deaths from cardiovascular disease showed no significant relationship either based on ginseng intake or intake frequency. Although American adults with hypertension have been taking ginseng recently,[22] this study did not show ginseng intake had a positive effect on blood pressure or deaths from cardiovascular disease.[23]

Deaths from other diseases excluding cancers and cardiovascular disease showed similar hazard ratios (age adjusted HR = 0.86; 95% CI, 0.79–0.97) as ginseng intake decreased the mortality risk of all-cause deaths in men. Also, when the lag time analysis was taken, the mortality risk of male ginseng users for other diseases was statistically significantly lowered for all-cause deaths (multivariate adjusted HR = 0.76; 95% CI, 0.65–0.88). We cannot present a clear perspective on why the mortality risk of male ginseng users was lower for other diseases than for cancers or cardiovascular diseases. Many *in vitro* and animal studies have suggested that the metabolic effects relate to the adaptation of homeostatic mechanisms resulting from exposure to stress, increased adrenal responsiveness, enhancing immunologic function, immunostimulatory activity in the aged, and antioxidant activity.[4,23] More double-blind randomized clinical trials and population-based studies would be required for an accurate conclusion.

There is a possibility that the effect of ginseng intake differs by sex. The all-cause mortality risk of male ginseng users was statistically significantly lower, but no such trend was shown in women. There was no association between cancer mortality and ginseng intake in men, whereas in the trend test for female ginseng users the cancer mortality risk decreased with a borderline significance as ginseng intake was increased. From the analysis of all-cause deaths, the efficacy of ginseng intake emerged in men after a certain lag time, but it did not in women. In the case-control study by Yun and Choi, the effect of ginseng against cancer was relatively lower in women than in men.[6] Since the effect of ginseng intake may differ by sex, it needs to be stratified and analyzed by sex. What causes sex differences in the effect of ginseng intake has not been clearly explained. Since there are reports that various ginsenosides and extracts from ginseng influence cytochrome P450 (CYP) enzyme activity,[24,25] sex differences in the expression of CYP enzyme in human tissues[26] might result in sex differences in the effect of ginseng intake.

This is the first study to examine the association between ginseng intake and mortality in the general population. The effect of ginseng intake was assessed through an 18.8-year prospective study, and almost all subjects were followed up. When data were collected, trained surveyors visited subjects to help them prepare the questionnaire instead of sending a simple questionnaire to them and also measured their height, weight, and blood pressure directly. Thus the probable information bias due to self-report was minimized.[12,13]

There were several limitations to our study. First, information on the frequency, duration, and amount of ginseng intake was not collected in detail. Potential misclassification might introduce bias measuring the effect of ginseng intake. Since it was a nondifferential misclassification not related to deaths, it is possible that any association with mortality was wrongly concluded to be insignificant. In this study, the relationship of ginseng intake with deaths was not clearly shown among frequent users, which might have been caused by the nondifferential misclassification. The case-control study[6,7] and cohort study[8] by Yun and Choi and the cohort study in China[9,10] were all conducted later than the Kangwha Cohort Study; in those studies, ginseng intake was examined in more detail, but outcomes did not include the effects of intake frequency and intake duration. Meanwhile, based on the outcome of a cohort study conducted in the same region as this study,[8] we estimated the frequency of ginseng intake in this study to be 1–11 times per year in infrequent users and at least once per month in frequent users. Second, this study did not collect information on species and types (eg, red, white, powder, tea) in detail. The difference in ginsenoside composition among various species of ginseng is important in assessing effect and efficacy.[27] It has been suggested that red ginseng may contain the most active cancer preventive components.[27] But we could not examine the effect on mortality by species and type of ginseng. Third, during 18.8 years of follow-up after the initial survey, subjects were not interviewed about how ginseng intake and other potential confounders had changed. As their physical conditions or other factors had evolved, the pattern of ginseng intake and confounders might have changed. Fourth, in this study, ginseng intake lowered the risk of all-cause deaths in men, while its preventive effect on deaths was weak. Residual confounding by unmeasured variables or measurement error may be the reason. Fifth, only a small number of studies have examined the preventive effect of ginseng intake on mortality and thus much stronger evidence is required to confirm any effects.[28] Therefore, readers of this report should be careful to understand this study.

In conclusion, this progressive cohort study over 18.8 years showed that ginseng intake decreased all-cause mortality in elderly males, but no similar effect was found in women. Cardiovascular disease deaths and ginseng intake were not related in both men and women. In women ginseng intake decreased cancer mortality risk, but insignificantly.

Disclosure Statement

No competing financial interests exist.

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Address correspondence to:
John Alderman Linton, M.D.
Department of Family Medicine
Yonsei University College of Medicine
134 Sinchon-dong, Seodaemun-gu
Seoul 120-752
Republic of Korea

E-mail: yohan@yuhs.ac

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