Non-organ Specific Cancer Preventive Effect of Korean Ginseng : A Prospective Study for 10 Years

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ABSTRACT

A prospective study was conducted to evaluate the preventive effect of Korean ginseng against cancer in the population residing ginseng cultivation area, Kangwha-eup from August 1987 to December 1997. The participants consisted of 4,553 adults over 40 years old who completed a questionare on ginseng intake.

During the surveillance period, 14.4% (656 of 4,553) of subjects had died, cancer accounting for 23.9% (157) of total deaths. The proportional hazard model of Cox was used to estimate relative risks when controlling simultaneously for covariates.

Ginseng intakers had a decreased risk (relative risk(RR) =0.48, 95% confidence interval (CI) : 0.34-0.66) for cancer compared with non-intakers. The RRs of cancer were 0.36 (95% CI: 0.24-0.56) for multiple combination intakers. Among 24 red ginseng intakers, there were no cancer deaths. The RRs of ginseng intakers were 0.38 (95% CI: 0.20-0.71) in gastric cancer and 0.29 (95% CI: 0.15-0.57) in lung cancer.

These findings strongly suggested Korean ginseng has non-organ specific cancer preventive effects against cancer. Further research for clarifying the mechanisms of prevention and clinical trials on Korean ginseng must be conducted with worldwide collaborations.

Introduction

Although immense advances have been made in basic scientific knowledge and in clinical treatment and cure of certain malignancies, the fact remains that the goal of substantial reduction in overall death rates for most of the common carcinomas, which account for most cancer deaths, has not been met. Recent analysis from National Cancer Institute (NCI) indicate that overall mortality from cancer in the United States actually rose from 1973 to 1992 would not achieve its stated target of a 50% reduction in cancer mortality by the year 2000 (1,2).

Fifty years have already passed since alkylating agents were first developed as cancer chemotherapeutics, but many cancers still remain difficult to cure (3). The failure to improve from 1 in 3 in the 1960s to 1 in 2 in the 1970 of 5 year "observed" survival stimulated awareness of the importance of chemoprevention and we have been trying to discover non-toxic cancer chemopreventive agents

among natural products since 1977 (4).

We hypothesized that the life-prolongation effect of ginseng described by Shennong during the Liang Dynasty in China may be due to the preventive activity of ginseng against the development of cancers (5). 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) (6). 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 tumors induced by chemical carcinogens in long-term (7,8) and medium-term anticarcinogenesis models using mice (9-12). We further investigated whether fresh ginseng has similar anticarcinogenic effects using Yun's 9 weeks medium-term anticarcinogenicity test (13-14). 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 (15). 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 (16). In 1987, we began to conduct a case-control study of 905 pairs (17) to confirm whether red ginseng extracts had as much anticarcinogenic effect as on mice. We extended the number of subjects for a case-control study to 1,987 pairs (18) from 905 pairs. The results showed a dose-response relationship in ginseng intakers and a marked decrease in risk for intakers of ginseng extracts and red ginseng, showing agreement with the result of the anticarcinogenic effects of red ginseng observed in animal experiments.

The aim of the prospective study is to investigate whether ginseng intake is related to the development of various cancers and to evaluate the preventive effect of ginseng in the population residing in ginseng cultivation area 6 month (in August 1987) after the first case-control study. Previous cohort study for morbidity and mortality (follow-up for 5 years) has been reported (19).

Present prospective study was conducted to evaluate the preventive effect of Korean ginseng against cancer in the population residing ginseng cultivation area, Kangwha-eup from August 1987 to December 1997 (follow-up for ten years).

Subjects and Methods

The study population was selected from persons who were listed in the 1987 resident' s 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 4,634 persons 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, life-long occupation, smoking and drinking habits, the 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. Fresh ginseng is less than four years old and can be consumed in the fresh state. White ginseng is grown for four to six years, and then peeled and dried to reduce the water content to 12% or less. Red ginseng is harvested after six years, and then steamed and dried. Each type of ginseng is further categorized into several forms of ginseng product. 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 three 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 life-long 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 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 inquiry. 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 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, prevalence data of Korea Medical Insurance

Corporation, etc. The diseases were classified by the first three digits of the International Classification of Diseases (20).

The Mantel-Haenszel procedure was used to estimate the relative risk (RR) of ginseng intake adjusted by age and sex (21, 22). 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 factor. All the regression equations included terms for age (three categories), sex, education (years of schooling grouped into four caterories), smoking and alcohol consumption. Data analyses were done by PC-SPSS version 6.1 statistical package (23).

Results

The study population consisted of 4,553 participants (male; 2,307, female; 2,246). Of 4,553 persons eligible for analysis, 70.7% were ginseng intakers in the past. The ginseng intake declined with age. There were statistically significant differences between groups with respect to all the subject characteristics. Participants who consumed ginseng were more educated, and smoked and drank less. Among cancer cases, 48.5% were ginseng intakers. They had a decreased risk (RR=0.48, 95% CI: 0.34-0.66) for cancer compared with non-intakers. On the type of ginseng, the RRs of cancer were 0.36 (95% CI: 0.24-0.54) for intakers of multiple combinations. The RRs for other types of ginseng showed a decreasing trend, but it was not statistically significant. Although the number of deaths for red ginseng intakers was 24 persons, there were no cancer deaths. A total of 656 deaths occurred during the period of August 1987 to December 1997. Cancer was the leading cause, accounting for 157 deaths (23.9%), followed by diseases of the circulatory system (135 deaths) and injury and poisoning (40 deaths). Among the cancer deaths, 41(6.3%) were due to gastric cancer, with 36(5.5%)occurring in the lung and 18 (2.7%) in the liver. The RR of total cancer mortality in the ginseng intake group was 0.48(95% CI: 0.34-0.66). The RRs of ginseng intakers were 0.38 (95% CI: 0.20-0.71) in gastric cancer and 0.29 (95% CI: 0.15-0.57) in lung cancer showing a statistically significant reduction. Among other diseases, there was association with ginseng intake in diseases of the circulatory system. There was a decrease in risk with rising frequency of ginseng consumed, showing a statistically significant dose-response relationship in lung cancer.

Discussion

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 tumors induced by chemical carcinogens in long-term (7,8) and medium-term anticarcinogenesis models using mice (9-12). We further investigated whether fresh

ginseng has similar anticarcinogenic effects using Yun's 9 weeks medium-term anticarcinogenicity test(13-14). 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.

A case-control study was carried out on 905 cases admitted to Korea Cancer Center Hospital in February 1987 in order to investigate the preventive effect of ginseng intake against cancer (17). The ginseng intakers had the RR of 0.56 (95% CI: 0.46-0.69) for cancer compared with non-intakers. There was a decrease in risk with the rising frequency and duration of ginseng intake. We also extended the study subjects to evaluate 1) the type of ginseng products that have the most prominent cancer preventive effect, 2) differences in preventive effect by sex, 3) the dose-response relationship by ginseng intake and 4) the type of cancer which can be prevented by ginseng (18). As a result, the RRs of cancer for males and females were 0.44 and 0.54 for ginseng intakers. Especially, the preventive effect of ginseng against cancer was observed in all types of ginseng product except fresh ginseng (silced and as juice) and white ginseng tea. This absence is consistent with results our previous case-control study (17) and the result of site, a medium-term bioassay system using pulmonary adenoma of the mouse (13,14). On the RRs for males and females increased in cancers of the lip, oral cavity and pharynx, stomach, colon and rectum, liver, and lung. However, there were inconsistent and weak associations between ginseng intake and cancers of the female breast and uterine cervix.

This cohort study was carried out on the population of 40-year-old residing in Kangwha-eup in August 1987 immediately after confirming preliminary results of the case-control studies. Among a total of 656 deaths, cancer was the leading cause, with 157 deaths (23.9%). On the other hand, according to 1996 death statistics published by the National Statistics Office of Korea (22), cancer deaths at over 40 years of age were 20.0%, showing the primary cause. In Kangwha-eup, 53.5% of 157 cancer cases had a history of ginseng intake in comparison with 71.4% of 4,396 noncases. This showed similar results in comparison with the proportion (74.5% and 69.6%) of control groups in the previous case-control study (17). The present study found a significant reduction of RR (0.48) between the intake of ginseng and cancer, as shown in the previous study (RR=0.56 and 0.50). On the type of ginseng, the RRs of cancer were 0.36 (95% CI: 0.24-0.54) for intakers of multiple combinations. The RRs for other types of ginseng showed a decreasing trend, but it was not statistically significant. However, preliminary cohort study (5-year follow-up) showed that the RR of cancer was 0.31 (95% CI: 0.13-0.74) for fresh ginseng extract intakers (19). Among 24 red ginseng intakers, there was no cancer death in both previous (19) and present cohort study, which are consistent with reduced RRs of latest case-control study (18,26) and findings of anticarcinogenicity of type and age of Korean ginseng (13,14).

On the site of cancer, among 157 cancer deaths during the ten-year follow-up period, stomach cancer was 41 (26.1%), lung cancer 36 (22.9%) and liver cancer 18 (11.5%). These order was similar

to the order of mortality rate in cancers of stomach, liver and lung in Korea (24). The RRs of ginseng intakers were 0.38 (95% CI: 0.20-0.71) in gastric cancer and 0.29 (95% CI 0.15-0.57) in lung cancer. These RRs were similar to five-year follow-up results (19).

In case-control studies for 905 pairs and 1,987 pairs, intake of ginseng extract decreased in risk remarkably than intake of fresh ginseng and showed a dose-response relationship according to frequency of ginseng intake. The RRs of ginseng intakers decreased in all kinds of cancers. The Lancet (25) stated in the editorial that although organ-specific 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 RR of ginseng intakers adjusted by economic status was 0.57 (95% CI: 0.47-0.70) compared with non-intakers. 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 (19). There was no significant relationship between ginseng intake by economic status. 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 intakers and non-intakers. This cohort removed selection and information biases in the case-control studies reported in 1990 and 1995. And this study 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.

Conclusion

Putting the present study, two case-control studies (17,18,27) and previous cohort study (5-year follow-up) (19,28) together, these results strongly suggest that Korean ginseng has a non-organ specific preventive effect against cancers. Further researches for clarifying the mechanisms of prevention and also for clinical trials on Korean ginseng must be conducted with worldwide collaborations.

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