Relationship between serum isoflavone concentrations and frequency of soybean products consumption in patients with prostate cancer

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ABSTRACT

Dietary consumption of high concentrations of soybean products has been suggested to reduce the risk for prostate cancer (PCa). We conducted a survey using patients with PCa to assess the relationship between serum concentrations of isoflavone aglycones and frequency of soybean products consumption in patients with PCa. We measured the serum concentrations of daidzein, genistein, glycitein, and equol in 99 PCa patients, in addition to conducting a survey using a self-administrated questionnaire that included the frequencies of various food item consumptions. If serum concentrations of equol were at a value less than 0.5 ng/mL, they were classified as an equol non-producer, and the other patients were classified as equol producers. As a result, serum concentrations of daidzein, genistein, and glycitein were found to be significantly correlated to each other ($P<0.001$). The frequency of tofu (soybean curd) consumption was significantly correlated with the serum concentration of daidzein ($P<0.05$). Likewise, the frequency of natto (fermented soybean) consumption was significantly correlated with the serum concentrations of daidzein, genistein, and glycitein ($P<0.01$). In the study there were 40 equol producers and 59 equol non-producers, but none of the food items were significantly different between the equol producers and the equol non-producers. We have a plan to perform a similar survey for population-based controls in the future. Comparisons between the data of the PCa patients and the controls would give us more information about the role of isoflavones and equol production in regard to the risk of PCa.

Key words : Prostate cancer, Genistein, Daidzein, Equol, Soybean products

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INTRODUCTION

Dietary consumption of high concentrations of soy products has been epidemiologically suggested to reduce the risk for prostate cancer (PCa)[1,2]. Isoflavone aglycones such as daidzein, genistein, and glycitein have also been shown to prevent PCa in vitro studies[3-7]. Furthermore, equol, the metabolite of daidzein in gut microflora, has been indicated to have potent anti-carcinogenic effects on PCa as well[8,9].

We conducted this survey using patients with PCa to assess the relationship between serum concentrations of isoflavone aglycones and the frequency of soy product consumption in patients with PCa. We also assessed whether dietary habits would influence the metabolism of isoflavones in soybean products, because the previous articles[10-15] reported that some dietary habits might be related to equol production in human gut microflora.

METHODS

There were 168 PCa patients who visited the Department of Urology, Sapporo Medical University from January, 2007 to April, 2008. We excluded 26 patients from the study, because 5 patients died, 19 patients were in too poor health, 1 subject moved out of the Hokkaido Prefecture, and 1 subject was not Japanese. Among the residual 142 patients, informed consent was obtained from 117 patients (82.3%), and their sera were collected. Their concentrations of isoflavone aglycones such as daidzein, genistein, glycitein and equol were measured by the LC-MS methods (SRL Co., Tokyo). If their concentrations of equol were at a value less than 0.5 ng/mL, they were classified as an equol non-producer. The other patients whose equol concentrations were at a value higher than or equal to 0.5 ng/mL, they were classified as equol producers. Furthermore, all of the 117 patients also fulfilled the self-administrated questionnaire which included items about frequencies of consumption for 28 foods and their lifestyle habits over the period of one or two years before their diagnosis.

The average age at the time of diagnosis of the 117 patients with PCa was 69.4 years (standard deviation or SD; 6.4 years; Range; 53.6-82.2 years). The average interval between the date of the diagnosis and filling out the questionnaire was 1.5 years (SD; 1.1 years; Range 0～7.3 years), and the average interval between the date of taking the sera and filling out the questionnaire was 35.0 days (SD; 35.7 days; Range; 0～157 days). Among them, 79 patients had been operated on with a radical prostatectomy, 34 patients had been treated with radiation, and 14 patients had been treated with hormone therapy.

Furthermore, 18 patients had cancer in other sites such as the stomach (6 cases) or intestine (3 cases). We excluded these 18 patients from the analysis because of a possibility in malnutrition. Eventually, we analyzed the data of 99 PCa patients. The software SAS (ver. 9.2) was used for the analysis. The significance level was set at a 5% level.

RESULTS

As shown in Table 1, the median (ng/mL) of daidzein, genistein, glycitein, and equol were 118.9, 134.5, 3.3; and a value less than 0.5, respectively. As the Spearman's correlation coefficients are shown in Table 2, serum concentrations of daidzein, genistein, and glycitein were significantly correlated to each other ($P<0.001$). However, the serum concentration of equol was

Table 1. Distribution in serum levels of isoflavone aglycones among the 99 prostate cancer patients.

	Median (ng/mL)	Range (ng/mL)
Daidzein	72.4	1.3-967.2
Genistein	134.5	3.2-2134.7
Glycitein	3.3	0.5-48.8
Equol	a value less than 0.5	a value less than 0.5-164.2

not correlated with any serum concentration of daidzein, genistein, or glycitein.

As shown in Table 3, the frequency of tofu (soybean curd) consumption was significantly correlated with serum concentrations of daidzein ($P<0.05$). Likewise, the frequency of natto (fermented soybean) consumption was significantly correlated with serum concentrations of daidzein, genistein, and glycitein ($P<0.01$). Frequencies of other soybean product consumption such as miso soup, fried soybean curd (aburage), sprouted soybean (moyashi), green soybean (edamame), and (soybean milk) were not correlated with any serum concentrations of isoflavone aglycone.

Under our classification there were 40 equol producers and 59 equol non-producers. We compared the frequencies of various food item consumptions between the equol producers and the equol non-producers, and calculated the odds ratios and their 95% confidence intervals adjusting age with the logistic regression model. As shown in Table 4, none of the food items were significantly different between the equol producers and the equol non-producers.

DISCUSSION

Frequencies of soybean curd or fermented soybean consumption in PCa patients one or two years before the diagnosis were significantly correlated with serum concentrations of daidzein, genistein, and glycitein. These results suggest that dietary habits might have lasted even after the diagnosis of cancer was made.

Dietary habits have been suggested to influence the metabolism of isoflavones and the production of equol[10-15]. Setchell and Cole[13] showed that the proportion of equol producers in vegetarians was 59%, similar to the reported frequency in Japanese adults consuming soybean products, and much higher than that for non-vegetarian adults. Lampe et al.[14] also reported that higher dietary fibers and plant protein, less fat, and more carbohydrate intakes have been associated more strongly with equol producers than equol non-producers among female patients. Miyanaga et al.[15] have suggested that higher consumption of soybean products and green tea can enhance equol production.

On the contrary, Zhao et al.[16] did not show any correlation between the equol excretion and intakes of food items among Japanese patients.

Table 2. The Spearman's correlation coefficients in serum levels of isoflavone aglycones among the 99 prostate cancer patients.

	Daidzein	Genistein	Glycitein
Genistein	0.927***	-	-
Glycitein	0.915***	0.817***	-
Equol	-0.055	-0.013	-0.033

*** : $P<0.001$

Table 3. The Spearman's correlation coefficients between serum levels of isoflavone aglycones and frequency of soybean product consumptions among the 99 prostate cancer patients.

Food items	Daidzein	Genistein	Glycitein	Equol
Miso soup	0.118	0.056	0.085	0.193
Soybean curd (Tofu)	0.214*	0.181	0.157	0.042
Fermented soybean (Natto)	0.302**	0.285**	0.309**	0.025
Fried soybean curd (Aburage)	-0.031	-0.031	0.008	-0.123
Sprouted soybean (Moyashi)	-0.043	0.042	0.093	0.052
Green soybeans (Edamame)	-0.090	-0.052	0.041	0.011
Soy milk (Tonyu)	-0.098	-0.058	-0.103	0.017

** : $P<0.01$ * : $P<0.05$

Table 4. Age-adjusted odds ratios (ORs) and their 95% confidence intervals (95%CIs) of frequency of food item comsuptions in the equol producers (n=40) compared with the equol non-producers (N=59) among the 99 prostate cancer patients.

Food items	OR#	95%CI
Chiken	0.76	0.47-1.24
Beef or pork	0.64	0.38-1.08
Ham, sousage	0.72	0.45-1.14
Fish	1.00	0.70-1.43
Seaweed	0.86	0.65-1.16
Miso soup	1.23	0.94-1.60
Soybean curd (Tofu)	0.99	0.66-1.40
Fermented soybean (Natto)	0.97	0.75-1.25
Fried soybean curd (Aburage)	0.80	0.50-1.27
Sprouted soybean (Moyashi)	1.14	0.72-1.81
Green soybeans (Edamame)	0.90	0.51-1.61
Soy milk (Tonyu)	0.92	0.64-1.31
Carrot	0.96	0.68-1.34
Broccori	1.07	0.78-1.46
Tomato	0.95	0.73-1.23
Green or yellow vegetables	1.00	0.78-1.28
White vegetables	1.22	0.91-1.64
Orange	0.98	0.75-1.28
Other fruits	0.84	0.64-1.09
Milk	1.00	0.82-1.21
Yogurt	0.89	0.72-1.10
Green tea	1.02	0.86-1.21
Coffee	1.03	0.86-1.24
Black tea	0.76	0.53-1.09

: Odds ratio per 1 order among 8 orders of frequency of food consumption.

Our results did not exhibit any association between the equol producers and the equol non-producers either. One of the reasons for such no association may be that most Japanese patients eat soybean products, and therefore, the differences were reduced.

Our data of serum concentrations in PCa patients were collected during non-fasting periods rather than during fasting periods. Moreover, some of the cases had been treated with radiation or hormonal therapy. These factors might have influenced the serum concentrations of isoflavones.

Because our data about frequencies of various food item consumptions were focused on dates one or two years before the diagnosis, it could be possible that recall bias might have existed. In the future we plan to perform a similar survey for population-based controls who do not have any cancer. Comparison between the data of PCa patients and the controls would give us more information about the role of isoflavones and equol production in regard to the risk of PCa.

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REFERENCES

1. Mori M, Masumori N, Fukuta F, Nagata Y, Sonoda T, Sakauchi F, Ohnishi H, Nojima M, Tsukamoto T. Traditional Japanese diet and prostate cancer. Mol Nutr Food Res 2009; 53: 191–200.
2. Par S-Y, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Legume and isoflavone intake and prostate cancer risk: The Multiethnic Cohort Study. Int J Cancer 2008; 123: 927–932.
3. Hikasaka A, Asamoto M, Hokaiwado N, Kato K, Kuzutani K, Kohri K, Shirai T. Inhibitory effects of soy isoflavones on rat prostate carcinogenesis induced by 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP). Carcinogenesis 2004; 25: 381–387.
4. Handayani R, Rice L, Cui Y, Medrano TA, Samedi VG, Baker HV, Szabo NJ, Shiverick KT. Soy isoflavones alter expression of genes associated with cancer progression, including interleukin-8, in androgen-independent PC-3 human prostate cancer cells. J Nutr 2006; 136: 75–82.
5. Raschke M, Rowland IR, Magee PJ, Pool-Zobel BL. Genistein protects prostate cell against hydrogen peroxide-induced DNA damage and induces expression of genes involved in the defense against oxidative stress. Carcinogenesis 2006; 27: 2322–2330.
6. Hedlund TE, van Bokhoven A, Johannes WU, Nordeen SK, Ogden LG. Prostate fluid Levels of isoflavonoids in soy consumers are sufficient to inhibit growth of benign and malignant prostatic epithelial cells in vitro. Prostate 2006; 66: 557–566.
7. Lakshman M, Xu L, Ananthanarayanan V, Cooper J, Takimoto CH, Helenowski I, Pelling JC, Bergan RC. Dietary genistein inhibits metastasis of human prostate cancer in mice. Cancer Res 2008; 68: 2024–2032.
8. Hedlund TE, Johannes WU, Miller GJ. Soy isoflavonoids equol modulates the growth of benign and malignant prostatic epithelial cells in vitro. Prostate 2003; 54: 68–78.
9. Lund TD, Munson DJ, Haldy ME, Setchell KD, Lephart ED, Handa RJ. Equol is a novel anti-androgen that inhibits prostate growth and hormone feedback. Biol Reprod 2004; 70: 1188–1195.
10. Akaza H, Miyanaga N, Takashima N, Naito S, Hirao Y, Tsukamoto T, Mori M. Is daidzein non-metabolizer a high risk for prostate cancer? ; A case-controlled study of serum soy beans isoflavones concentration. Jpn J Clin Oncol 2002; 32: 296–300.
11. Akaza H, Miyanaga N, Takashima N, Naito S, Hirao Y, Tsukamoto T, Fujioka T, Mori M, Kim W-J, Song JM, Pantuck AJ. Comparisons of percent equol producer between prostate cancer patients and controls: Case-controlled studies of isoflavones in Japanese, Korean, and American residents. Jpn J Clin Oncol 2004; 34: 86–89.
12. Yuan JP, Wang JH, Liu X. Metabolism of dietary soy isoflavones to equol by human intestinal microflora-implications for health. Mol Nutr Food Res 2007; 51: 765–781.
13. Setchell KDR, Cole SJ, Method of defining equol-producer status and its frequency among vegetarians. J Nutr 2006; 136: 2188–2193.
14. Lampe JW, Karr SC, Hutchins AM, Slavin

JL. Urinary equol excretion with a soy challenge: Influence of habitual diet. Proc Soc Exp Biol Med 1998; 217: 335–339.
15. Miyanaga N, Akaza H, Takashima N, Nagata Y, Sonoda T, Mori M, Naito S, Hirao Y, Tsukamoto T, Fujioka T. Higher consumption of green tea may enhance equol production. Asian Pacific J Cancer Prev 2003; 4: 297–301.
16. Zhao JH, Sun SJ, Arao Y, Oguma E, Yamada K, Horiguchi H, Kayama F. Identification of equol producers in a Japanese population by high-performance liquid chromatography with coulometric array for determining serum isoflavones. Phytomedicine 2006; 13: 304–309.

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