MINI-REVIEW

Soybeans, Soy Foods, Isoflavones and Risk of Colorectal Cancer: a Review of Experimental and Epidemiological Data

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Abstract

Incidence rates of colorectal cancer are relatively low in Asian populations, in which soy foods are commonly consumed. Soybeans and soy foods are an almost exclusive source of isoflavone intake. In *in vitro* studies, isoflavones have been shown to have various anticarcinogenic properties such as inhibition of protein tyrosine phosphorylation, induction of apoptosis, antiangiogenesis, and inhibition of DNA topoisomerase. Thus the protective role of soy foods and isoflavones in the etiology of colorectal cancer is a matter of interest. We therefore reviewed animal and epidemiological studies of colorectal cancer in relation to soybeans, soy foods, and isoflavones. Animal studies fairly consistently showed that soyfoods or isoflavones inhibited the formation of aberrant crypt foci, but did not clearly demonstrate an inhibitory effect of soy foods and isoflavones on the development of chemically-induced colorectal cancer. Several case-control studies have suggested that soy food consumption may confer a reduced risk of colorectal cancer although the findings are rather inconsistent. Most of the previous studies, especially in Japan, ascertained only the frequency of consuming selected soy foods, and thus were defective as regards the measurement of the total consumption of soy foods. Further epidemiological studies are needed to clarify the role for soy foods in colorectal carcinogenesis.

Key Words: Colorectal cancer - soybean - soy foods - isoflavones

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Introduction

A weak estrogenic effect of isoflavones, which also exert an antiestrogenic actions, has caused much interest in the role of soyfoods in the prevention of hormone-related cancers such as breast cancer and prostate cancer (Bingham et al., 1998). Soy foods are an almost exclusive dietary source of isoflavone intake, and genistein and daidzein are predominant soyfood isoflavones (USDA-Iowa State University Isoflavones Database, 1999). A small amount of glycitein is also contained in soyfoods, but biological effects of glycitein have not been studied in detail. In addition to the hormonal effects, a wide variety of anticarcinogenic properties of isoflavones, especially genistein, have been noted in the past decade. Genistein is known to inhibit the growth of a wide range of human and rodent cell lines including human colon cancer cell lines (Yanagihara et al., 1993; Kuo, 1996). The *in vitro* inhibition of cancer cell growth by genistein has been linked with the inhibition of tyrosine protein kinases (Akiyama et al., 1987), induction of apoptosis (Spinozzi et al., 1994), antiangiogenetic effects (Fotsis et al., 1993), and inhibition of DNA topoisomerase (Okura et al., 1988).

Colorectal cancer is the fourth most common incident cancer in the world, showing a wide inter-country variation. The incidence of colorectal cancer as well as of breast cancer and prostate cancer is relatively low in Asian populations (Parkin et al., 1999), in which soy foods are commonly consumed. In addition, Japanese immigrants in the United Status show incidence rates of colorectal cancers very near to the rates among the whites in the country (Flood et al., 2000). Thus the protective effect of soyfoods and isoflavones is a matter of interest in the etiology of colorectal cancer. We reviewed animal and epidemiological studies of colorectal cancer in relation to soybeans, soy foods, and isoflavones.

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Isoflavones: Occurrence and Intake

Isoflavones in plant foods are mostly in the form of glycosides, which are conjugated with a glucose, biologically inactive, and not absorbed through the intestinal wall (Miksicek, 1995). The glycoside forms of genistein, daidzein, and glycitein are called genistin, daidzin, and glycitin, respectively. Intestinal bacteria deconjugate the glycosides to aglycones (Kelly et al., 1993). Fermented soy products such as miso contain more unconjugated isoflavones rather than glycosides (Coward et al., 1993). Genistein accounts for two-thirds or more of isoflavones in soy food, and most of the remaining isoflavones are daidzein; the content of glycitein is very small (USDA-Iowa State University Isoflavones Database, 1999).

Intestinal absorption and metabolism of isoflavones have not been studied well in humans. Mostly based on animal studies, it is generally thought that absorbed isoflavones are reconjugated with glucuronide and sulfates in the liver, and excreted in the urine and bile (Bingham et al., 1998; Messina and Bennink, 1998; Messina, 1999). It is shown that intestinal microflora in sheep convert genistein to an inactive metabolite (p-ethylphenol) and daidzein to equol which also have an estrogenic action (Lindsay and Kelly, 1970).

Isoflavone contents in soy foods are variable in the range of 5-750 μg/g as summarized in Table 1 (Wakai et al., 1999; Reinli and Block, 1996; USDA-Iowa State University Isoflavones Database, 1999). The average intakes of isoflavones among adults in Japan were estimated to be 20-30 mg per day in one area (Nagata et al., 2001) and 40 mg per day in another area (Kimira et al., 1998). According to the National Nutrition Survey in 1995, per capita amounts of individual soy foods consumed per day were as follows: miso 14.0 g, tofu and tofu products 46.7 g, soybeans and processed soybeans 7.4 g, and soy sauce 21.6 g. By using the approximate contents of isoflavones in these foods as described by Wakai et al. (1999), the average intake is estimated to be 30 mg per day. People in China seem to consume almost the same amount of isoflavones as those in Japan. Chen et al. (1999) reported that total intake of isoflavones was 40 mg/day in Shanghai, which was estimated from six groups of soy products. On the other hand, Seow et al. (1998) reported that the mean intake of isoflavones was 33 mg per week in Chinese in Singapore based on a dietary survey of five soy food items. People in Western countries have the possibility of consuming isoflavones from food additives including soy protein isolate and soy protein concentrate as other sources (Lampe et al., 1999). However, urinary excretion of isoflavones was shown to be 15-30 times lower in the United States and England than in Japan (Adlercreutz et al., 1995; Cassidy et al., 1991). Further, plasma concentrations of isoflavones in Finnish were as low as one-tenth of those of Japanese (Adlercreutz et al., 1992; Adlercreutz et al., 1993; Arai et al., 2000)

Animal Studies

As summarized in Table 2, much work has recently been done regarding the effect of soy products or isoflavones in the development of colonic aberrant crypt foci (ACF) in rats

Table1. Isoflavone Contents in Soy Foods on a Wet Weight Basis

Soy foods	Wakai et al. (1999)		Reinli and Block (1996)		USDA-IOWA State University (1999)	
	Daidzein (μg/g)	Genistein (μg/g)	Daidzein (μg/g)	Genistein (μg/g)	Daidzein (μg/g)	Genistein (μg/g)
Soy beans, dry	360	587	NA	NA	NA	NA
Soy beans, green	546	729	546	729	678	725
Soy beans, boiled	118	244	NA	NA	270	278
Soy bean sprouts	175	268	138	230	NA	NA
Tofu (soybean curd)	85	156	76	166	99[a)]	161[a)]
Tofu, freeze dried	225	297	NA	NA	253	422
Fried tofu, thin	187	228	NA	NA	178	280
Fried tofu, thick	74	185	NA	NA	NA	NA
Ganmo[b)]	186	233	NA	NA	NA	NA
Soy milk	37	71	18	26	45	61
Okara (tofu refuse)	18	41	NA	NA	54	65
Natto (fermented soybeans)	302	372	NA	NA	219	290
Miso (soybean paste)	298	468	266	376	161	246
Soy sauce	14	8	8	5	9	8

NA: not available

[a)] The value is the average of five reported concentrations of three types of tofu.

[b)] Fried tofu and minced vegetables/seaweed.

Table 2. Effects of Soy Foods and Isoflavones on Colonic Aberrant Crypt Foci (ACF) in Carcinogen Treated Rats

Author (year)	Carcinogen /total doses	Contents (per 100g diet)		No. of ACF[a)]
Masaoka et al. (1998)	AOM 45 mg/kg s.c.	Miso	0%	138
			10%	86*
Monsma et al. (1997)	DMH NA	Beef protein	18%	189
		Soy protein isolate	18%	138*
Pereira et al. (1994)	AOM 30 mg/kg s.c.	Geny3tein	0 mg	85.3
			7.5 mg	60.3*
Helms and Gallaher (1995)	NA	Genistein	0 mg	7.2[b)]
			37 mg	4.7*[b)]
Thiagarajan et al. (1998)	AOM 30 mg/kg s.c.	Genistein	0 mg	133
			15 mg	77*
Davies et al. (1999)	AOM 30 mg/kg s.c.	Isoflavones	2 mg	5.0
			57 mg	2.8
Gee et al. (2000)	DMH 60 mg/kg s.c.	Genistein	0 mg	No difference
			25 mg	

*P<0.05
NA: not available
[a)] Number of ACF per colon unless otherwise specified.
[b)] Number of aberrant crypts per cm^2

given a chemical carcinogen. ACF are preneoplastic lesions of colorectal cancer, although the lesions may be reversible (Bird and Good, 2000). At least five studies showed a statistically significant effect of soy diet or isoflavone supplement inhibiting the formation of ACF (Masaoka et al., 1998; Monsma et al., 1997; Pereira et al., 1994; Helms and Gallaher, 1995; Thiagarajan et al., 1998). A dose-dependent inhibitory effect was reported in three studies (Masaoka et al., 1998; Pereira et al., 1994; Helms and Gallaher, 1995). Thiagarajan et al. (1998) also reported that a soy-product diet containing 0.049% genistein primarily in the form of glycosides showed a less inhibitory effect in the formation of ACF than a diet supplemented with 0.015% genistein in the form of aglycone. These findings suggest that isoflavones as aglycones may be more effective than glycosides as regards anticarcinogenicity.

On the other hand, two studies failed to show an inhibition of ACF formation by isoflavone supplement. In the study reported by Davies et al. (1999), control diet was of extremely Westernized type containing fat equivalent to 40% of caloric and low calcium (65 mg per 100g diet). Gee et al. (2000) performed two experiments with genistein or soy protein isolate given at different periods. The administration of genistein or soy protein isolate prior to the injection of dimethylhydrazine (DMH) increased the formation of ACF by 2-3 folds, while there was no effect of genistein or soy protein isolate after the treatment of DMH.

Most of the animal experiments have not shown an evident, protective effect of soybean products given as a source of protein in chemically-induced colorectal tumorigenesis (Clinton et al., 1979; McIntosh et al., 1995; Monsma et al., 1997). The incidence of colorectal tumors induced by DMH was not lower in rats fed soy protein than in those fed meat protein (McIntosh et al., 1995; Monsma et al., 1997). In the former study (McIntosh et al., 1995), the total number of intestinal and colorectal tumors was rather greater in the group of soy protein than in the group of meat protein. One study reported that diets of soybean curd refuse and insoluble-molecular weight of soy protein digest, compared with casein diet, resulted in lower frequencies of colorectal tumors in rats treated by azoxymethane (AOM) and subsequently by deoxycholate as a cancer-promoting agent (Azuma et al., 1999). A diet of soy protein isolate containing 43mg of isoflavones per 100g diet substantially decreased AOM-induced colorectal tumors in F2 generation of rats, with their parents fed the same diet before mating (Hakkak et al., 2001). An isoflavone-rich diet (50-60mg per 100g diet) did not show an inhibitory effect in either AOM-treated rats or the *Min* mouse (Davies et al., 1999; Sorensen et al., 1998). The *Min* mouse has a heterozygous mutation of the *APC* gene, the murine homologous of the human *APC* gene, and is the model for human familial adenomatous polyposis coli. Rao et al. (1997) found no difference in the incidence of colorectal tumors induced by AOM between rats fed a genistein-supplement diet (25 mg genistein per 100 g diet) and control diet, but observed a greater number of tumors per tumor-bearing rat in the group of genistein supplement.

Anticarcinogenic effects of soy-related compounds other than isoflavones have also been a matter of interest in animal experiments. A soybean extract containing the Bowman-Birk protease inhibitor (BBI) was shown to inhibit colon tumorigenesis in DMH-treated mice; a diet containing 0.1% BBI resulted in approximately 45% reduction of colon adenocarcinomas (Billing et al., 1990). Because autoclaved BBI did not show an inhibitory effect in colon carcinogenesis, it was considered that protease inhibitory activity was necessary for tumor suppression. Further, it was reported that BBI concentrate of 0.5% in diet resulted in a 40-50% decrease in the number of tumors per mouse in the small intestine and colon in the *Min* mice (Kennedy et al., 1996).

Ecological Studies

Several Asian countries have the highest consumption of soy foods in the world. According to the Food Balance Sheets of the Food and Agriculture Organization (FAO, 1996), the per capita daily consumption of soybean product was highest in North Korea (24 g), followed by Japan (22 g), Indonesia (22 g), South Korea (17 g), and China (16 g); the consumption in other Asian countries ranged 0.0-5.8 g. Most countries in Europe, North America, and Oceania had almost null consumption of soybean products. The consumption of soy foods derived from the FAO Balance Sheets was not measurably correlated with colorectal cancer mortality in 38 countries (McKeown-Eyssen and Bright-See, 1984).

Using food consumption data by district in the National Nutrition Survey in Japan, Nagata (2000) reported that intakes of soy products and isoflavones were positively correlated with mortality from colorectal cancer; correlation coefficient for soy products were 0.32 in males and 0.44 in females, and those for isoflavones were 0.32 in males and 0.51 in females, after adjustment for total energy, alcohol, and other covariates, whereas the correlations were almost null without the adjustment. However, there was a serious methodological flaw in this study. Because data on food consumption were available only for 12 districts, which comprised of 1-6 prefectures, the consumption for each district was applied to the consumption for prefectures within the district. There is a large variation in colorectal cancer mortality by prefecture within each district; standardized

Table 3. Effects of Soy Foods and Isoflavones in the Occurrence of Colorectal Tumor in Rats

Author (year)	Species	Carcinogen /total doses	Contents (per 100g diet)		Incidence (%)	No. of tumor[a)]
Clinton et al. (1979)	Rat	DMH 225 mg/kg i.p.	Soy protein Beef protein	20% 20%	39 43	1.3 1.4
Mcintosh et al. (1995)	Rat	DMH 45 mg/kg s.c.	Defatted soybeans Red meat	33% 23%	60[b)] 55[b)]	2.1[c)] 1.0[*c)]
Monsma et al. (1997)	Rat	DMH NA	Beef protein Soy protein isolate	18% 18%	34 33	NA
Azuma et al. (1999)	Rat	AOM 45 mg/kg i.p.	Okara[d)] Soy protein Casein	50% 14% 10%	14% 25% 71%	1.0 1.0 1.4
Hakkak et al. (2001)	F2 rat	AOM 30 mg/kg s.c.	Soy protein isolate Casein		12** 50	NA
Rao et al. (1997)	Rat	AOM 30 mg/kg s.c.	Genistein	0 mg 25 mg	78 78	1.75 2.63*
Sorensen et al. (1998)	Min mouse	NA	Low isoflavones High isoflavones	2 mg 48 mg	NA	2.2[e)] 2.3[e)]
Davies et al. (1999)	Rat	AOM 30 mg/kg s.c.	Isoflavones	2 mg 57 mg	72.7 75.0	NA

*P<0.05 **P<0.01
NA: not available
[a)] Number of tumors per tumor-bearing rat unless otherwise specified.
[b)] Intestinal tumor
[c)] Number of tumors per rat.
[d)] Soy curd refuse
[e)] Data are shown for males only.

mortality ratios of male colon cancer by prefecture range 81 to 113 in the district with the maximum variation, and 92 to 100 in the district with the minimum variation (Tominaga and Oshima, 1999).

In view of the increasing trend in mortality from colorectal cancer since 1950s in Japan (Tominaga and Oshima, 1999), it is of interest to see the trend of soy food consumption in the country. According to the National Nutrition Survey (Ministry of Health and Welfare, 1997), the consumption of all soy foods combined has been fairly constant at the amount of around 90 g per day. Miso consumption has gradually declined while the consumption of tofu has increased (Figure 1). The trend of soy food consumption thus appears to be unrelated to the increasing trend of colorectal cancer mortality in Japan.

Case-control Studies

In Japan, four studies have examined the relation between selected soy foods and colorectal cancer (Table 4). The findings are inconsistent among studies as well as within studies. Miso soup was statistically nonsignificantly related to a decreased risk of colon cancer in two studies (Tajima and Tominaga, 1985; Nishi et al., 1997), but to an increased risk in one study (Hoshiyama et al., 1993). Three studies also showed a tendency of decreased risk of colon cancer in relation to the consumption of tofu and other soy foods (Watanabe et al., 1984; Hoshiyama et al., 1993; Nishi et al., 1997). As for rectal cancer, Watanabe et al. (1984) showed a statistically significant decrease in the risk among those with a high consumption of soybeans and tofu combined, and Hoshiyama et al. (1993) found a statistically significant decrease in the risk in association with the consumption of soy products as measured collectively. However, two studies

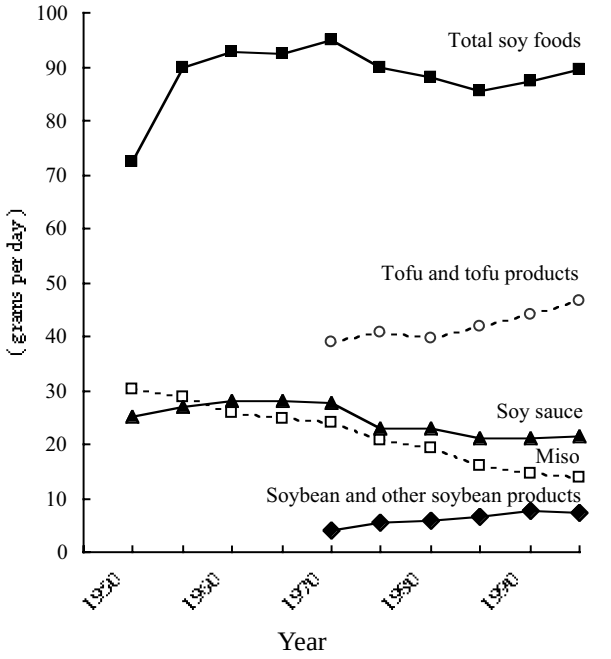

Figure 1. Per Capita Average Consumption (g/day) of Soy Foods in Japan, 1950-1995

Table 4. Case-control Studies on Soy Foods and Colorectal Cancer in Japan*

Study (year)	Site	No.†	Soy foods	Comparison	OR (95%CI)
Watanabe et al. (1984)	Colon	138:138	Beans and tofu	+ vs -	0.6 (0.2-1.9)
	Rectum	65:65	Beans and tofu	+ vs -	0.1 (0.0-0.9)
Tajima and Tominaga (1985)	Colon	42:42	Tofu	4+ vs <1/week	1.1 (p > 0.05)
			Miso soup	1+/day vs less	0.5 (p > 0.05)
	Rectum	51:51	Tofu	4+ vs <1/week	1.6 (p > 0.05)
			Miso soup	1+/day vs less	2.1 (p < 0.05)
Hoshiyama et al. (1993)	Colon	79:653	Soy products	8+ vs <5/week	0.6 (0.3-1.3)
			Miso soup	2+ vs <1 bowls/day	1.9 (0.8-4.4)
	Rectum	102:653	Soy products	8+ vs <5/week	0.4 (0.2-0.9)
			Miso soup	2+ vs <1 bowls/day	0.8 (0.4-1.6)
Nishi et al. (1997)	Colon	177:354	Tofu	3+/week vs less	0.8 (0.6-1.1)
			Deep-fried tofu	3+/week vs less	0.7 (0.5-1.1)
			Miso soup	3+/day vs less	0.7 (0.4-1.2)
	Rectum	153:306	Tofu	3+/week vs less	1.0 (0.7-1.5)
			Deep-fried tofu	3+/week vs less	1.2 (0.8-1.9)
			Miso soup	3+/day vs less	0.9 (0.5-1.6)

* All studies were based on consumption frequencies.
† Numbers of cases and controls.

showed no protective association between soy foods and rectal cancer (Tajima and Tominaga, 1985; Nishi et al., 1997). Even a statistically significant increase in the risk of rectal cancer was reported among those consuming miso soup daily (Tajima and Tominaga, 1985).

In China, Hu et al. (1991) ascertained the consumption of bean products and miso quantitatively. They reported an OR of 0.3 (95% confidence interval [CI] 0.2-0.7) for male rectal cancer in relation to the consumption of soy products (>9 versus <2 kg per year). A statistically significant association with soy products did not emerge in the multivariate analysis, however. Data on statistically nonsignificant associations for colon cancer and female rectal cancer were not presented.

In Hawaii, Le Marchand et al. (1997) also quantitatively measured the consumption of tofu, legumes, and soy products in a fairly large study of colorectal cancer. While tofu consumption was unrelated to the risk of colorectal cancer, the consumption of legumes and soy products combined was statistically significantly associated with a decreased risk in women, but not in men; after adjustment for age, family history, drinking, smoking and total calorie intake, odds ratios (OR) for the highest versus lowest quintile were 0.5 (95% CI 0.3-0.9) in women and 0.8 (0.5-1.2) in men. There have been two studies of colon adenomas, a precursor of colon cancer, in relation to soy foods. One study examined the relation of miso soup to sigmoid colon adenomas in Japan, reporting an OR of 0.77 for ≥2 versus <1 bowels per day (Kono et al., 1991). Another study in the United States found a significant dose-response relation between tofu and soybeans combined and colorectal adenomas; after adjustment for total calorie, saturated fat, and other covariates, ORs for null, 0.5, and ≥1.0 servings per week were 1.00 (referent), 0.85 (0.50-1.45), and 0.48 (0.24-0.95), respectively (Witte et al., 1996).

Prospective Studies

Only one prospective study has addressed the relation between soy foods and colorectal cancer. Hirayama (1990) ascertained consumption frequency of miso soup, and examined its relation to 552 colon cancer deaths and 563 rectal cancer deaths. Miso soup consumption was virtually unrelated to either colon or rectal cancer; age-adjusted relative risks of colon cancer and rectal cancer for daily versus non-daily intake of miso soup were 1.13 (95% CI 0.97-1.32) and 1.04 (0.89-1.21), respectively.

Discussion

Despite various anticarcinogenic properties observed in *in vitro* studies, animal studies have not clearly demonstrated an inhibition of tumor occurrence in the colorectum by the administration of soy diet or isoflavones, whereas the ACF formation in the colorectum has consistently been inhibited by soy food or isoflavone administration. Reasons for the inconsistency in animal studies are not clear. These studies varied in terms of the administration of soy diet of isoflaovones as well as of chemical carcinogens. It is rather surprising that some studies showed an increase in tumor occurrence by soy diet or isoflavones (McIntosh et al., 1995; Rao et al., 1997).

Case-control and cohort studies in Japan have been rather naive methodologically, although the results from some of the case-control studies are suggestive of a protective association between soy foods and colorectal cancer. Because these studies were not designed specifically to address the relation between soy food or isoflavone intake and colorectal cancer, the consumption of soy foods was not comprehensively measured. Thus the null association with a certain soy food item or group in these studies does not necessarily indicate the lack of a protective association between soy foods and colorectal cancer. The quantitative measurement is needed with regard to isoflavone and soy food intake, because isoflavone content varies substantially with different soy foods and because the amount of soybeans used for one serving differs by type of soy foods.

Fermented soy foods contain larger amounts of isoflavones in the form of aglycones. Because the aglycone form was shown to have a more potent inhibitory effect in the development of ACF (Thiagarajan et al., 1998), it may be argued that fermented, rather than non-fermented, soy foods are more important in the prevention of colorectal cancer. In this regard, the decline in miso consumption over the past decades in Japan could be linked with the increasing trend of colorectal cancer.

As shown in case-control studies of colorectal cancer and adenomas in the United States, it is quite possible that soy foods are protective in colorectal carcinogenesis (Le Marchand et al., 1997; Witte et al., 1996). Further epidemiologic studies are needed to clarify the role for soy foods in colorectal carcinogenesis.

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