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Review

Soy, isoflavones, and prostate cancer

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Prostate cancer has marked geographic variations between countries. Genetic, epigenetic, and environmental factors co-contribute to the development of the cancer. The association between dietary factors and prostate cancer has been investigated and one explanation for the low incidence of the cancer in Asia might be high consumption of fresh vegetables including soybean and its products. Soybean is a species of legume contain high amount of isoflavones including genistein, daidzein, glycitein, and equol, which have a prophylactic effect on prostate cancer. In this article, epidemiological and laboratory studies on the relationship between soybeans, isoflavones and prostate cancer are reviewed and large scale multiethnic epidemiological studies are recommended.

Keywords: Daidzein / Equol / Genistein / Isoflavones / Prostate cancer

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1 Introduction

Prostate cancer is the second most common cancer by incidence and the sixth most common cause of cancer death in men worldwide [1]. However the incidence of clinical prostate cancer varies widely between ethnic populations and countries. The different rates between countries are over 400-fold, with the highest in the USA (124.8/100 000, age standardized rate (ASR)) and the lowest in the Bangladesh (0.3/100 000 ASR) [2]. The high-risk countries with incidence of prostate cancer of more than 50/100 000 (ASR) include the USA, Canada, New Zealand, Australia, the Northwestern European countries (Iceland, Finland, Sweden, Norway, Belgium, Switzerland, France, Germany, and Luxembourg) and Caribbean region (Barbados, Puerto Rico, Bahamas, Trinidad, and Tobago). The Asian countries are considered to be a low-risk region. On the other hand, incidence of latent prostate cancer is similar worldwide. Comparative geographic–pathologic autopsy studies suggest that the different incidence of prostate cancer is not based on different initiation of malignant transformation, but on different promoting factors probably including genetic, epigenetic, and environmental influences in the postinduction progression [3]. It may also be partly attributed to differences in screening and early detection [1].

Although genomic factors are important in the aetiology of prostate cancer, environmental factors including diet have been presumed to play a key role in prostate carcinogenesis [4, 5]. The geographic differences in the incidence of clinical prostate cancer, the major burden of this cancer especially in high-risk countries and the comparative research on Asia immigrants constitute one of the basic arguments for the hypothesis that environmental factors play an important role in the etiology of prostate cancer. A main environmental factor, generally recognized as a major determinant of cancer incidence, is diet. Over the past decades, a cumulative body of epidemiological studies has provided information on the role of habitual diet and nutrients in relation to the risk of developing prostate cancer. However, up to date, the data from prospective studies have not established causal or protective associations for specific nutrients or dietary factors to prostate cancer [6, 7].

Adlercreutz [8] hypothesized that the high intake of soybean products may be partly responsible for the lower incidence of prostate cancer in Japanese men. In this article, the association of soybeans, isoflavones and prostate cancer risk are reviewed and recommendations for future epidemiological research are proposed.

2 Materials and methods

A search of the "PubMed" database was undertaken in February, 2008 using the following search terms: "prostate can-

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Abbreviations: AR, androgen receptor, **ASR,** age standardized rate; **CI,** confidence interval; **OR,** odds ratio; **RR,** relative risk

cer" or "prostatic cancer" or "prostate carcinoma" or "prostate tumor" and "soy" or "soybean" or "legume" or "phytoestrogens" or "isoflavones" or "isoflavonoid" or "genistein" or "daidzein" or "glycitein". A total of 34 075 references were found when searching for "prostate cancer" or "prostatic cancer" or "prostate carcinoma" or "prostate tumor" by "title" (searching "any field" resulted in 75 530 references and searching "keywords" led to 58 383 references). Prostate cancer studies related to "soy" by "any field" were a small proportion of the total at 0.3% (111/34 075). When the search was limited to "title", there were only 51 references for "genistein" but only 35 for "soy", 17 for "phytoestrogens", 14 for "isoflavones", 5 for "soybean", 3 for "daidzein", 2 for "isoflavonoid," and 1 for both "legume" and "glycitein". Other relevant sources such as references listed in published articles, electronic databases [2, 6] and books [1, 9, 10] are also included. The criteria for inclusion in the review are epidemiological studies providing data on dietary intake of soy, soy products or isoflavones, relative risk (RR) or odds ratio (OR), or laboratory studies with blood, prostate fluid or urinary measurements of isoflavones, and their relationship with prostate cancer. Cell culture and animal studies on possible anticancer mechanisms are also included.

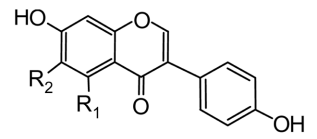
3 Results and discussion

3.1 Vegetables and phytoestrogens

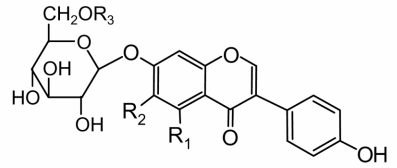
Vegetables and fruits are consumed from different parts of eatable plants, including the leaves, roots, tubers, flowers, stems, seeds, and shoots. In a balanced diet vegetables and fruits contribute to a wide variety of micronutrients, including vitamins and trace elements. They also contain a wide range of biologically active phytochemicals such as phytoestrogens, phytosterols, polyphenols, and sulfides [1]. Phytoestrogens are a diverse group of naturally occurring nonsteroidal plant compounds. Because of their structural similarity with estradiol (17β-estradiol), phytoestrogens have the ability to cause estrogenic or/and antiestrogenic effects [9]. They consist of four main classes: isoflavones, lignans, flavonoids, and coumestans. The best-researched group is the isoflavones, which are commonly found in soybeans and soy products. Lignans mainly originate from whole grain products. Flavonoids are found in high concentrations in a variety of fruits, vegetables, and tea. Clover and alfalfa sprouts, refried beans, and pinto beans are the major dietary sources of coumestans [11].

3.2 Legumes, soybeans, and isoflavones

Legumes are the seeds of plants from the leguminosae family and soybean is a species of legume native to Eastern Asia. Soy protein is now recognized as a "complete" protein with a protein digestibility – corrected amino acid score of



R_1	R_2	aglycones
H	H	daidzein
OH	H	genistein
H	OCH_3	glycitein



R_1	R_2	R_3	glucoside
H	H	H	daidzin
OH	H	H	genistin
H	OCH_3	H	glycitin
			acetylglucoside
H	H	$COCH_3$	acetyldaidzin
OH	H	$COCH_3$	acetylgenistin
H	OCH_3	$COCH_3$	acetylglycitin
			malonylglucoside
H	H	$COCH_2COOH$	malonyldaidzin
OH	H	$COCH_2COOH$	malonylgenistin
H	OCH_3	$COCH_2COOH$	malonylglycitin

Figure 1. The chemical structure of common isoflavones [15].

one, equivalent to the golden standard, and egg albumin [12]. Soy is a good source of phytochemicals (especially the isoflavones in soy), dietary fiber, oligosaccharides, and minerals. Soybeans are also rich sources of lipids (≈18–20% by weight) and contain saturated, monounsaturated, and PUFAs (15, 23, and 58% of total fat, respectively). The most common PUFAs in soybean are linoleic acid (18:2*n*–6; 51% of total fat) and α-linolenic acid (18:3*n*–3; 7%) [10]. Table 1 displays the contents of protein and isoflavone in selected soy products [12]. Tofu or bean curd is an unusual food with a custard-like texture made from soybeans and originally developed by the Chinese people in the Han Dynasty (206 BC – AD 200).

Isoflavones differ from flavones in that the benzyl ring B is linked to position 3 instead of position 2 [13] and are found in foods such as soy, lentils, beans, and chickpeas [14]. Soybeans contain three types of isoflavones, as four chemical forms (aglycons, glycosides, acetylglucosides, and malonylglucosides), see Fig. 1. The major aglycons are daidzein, genistein, and glycitein. The major glycosides are genistin, daidzin, and glycitin. The acetylglucosides include 6″-*O*-acetyldaidzin, 6″-*O*-acetylgenistin, and 6″-*O*-acetylglycitin and the malonylglucosides contain 6″-*O*-

Table 1. Protein and isoflavone contents of selected soy products[a)] [12]

Food	Serving size			Soflavone content	
	Weight (g)	Volume	g/100 g protein	mg/g protein	mg/serving
Mature soybeans, uncooked	47	1/4 cup	37.0	5.1	87.8
Roasted soybeans	43	1/4 cup	35.2	5.5	83.5
Soy flour	21	1/4 cup	37.8	5.5	43.8
Textured soy protein, dry	30	1/4 cup	6.0	5.2	94.0
Green soybeans, uncooked	128	1/2 cup	16.6	3.3	70.1
Soymilk	228	1 cup	4.4	2.0	20.0
Tofu, uncooked	114	4 oz	15.8	2.1	38.3
Soy protein isolate, dry	28	1 oz	92.0	2.2	56.5
Soy concentrate, dry	28	1 oz	63.6	0.3	12.4

a) Values are representative and presented for illustrative purposes; values were obtained from the published literature and from chemical analyses by authors obtained for selected products. The isoflavone content varies widely among soybean varieties and from product to product depending on the manufacturing process and source of soy protein.

malonyldaidzin, 6″-*O*-malonylgenistin, and 6″-*O*-malonylglycitin [15, 16]. Some legumes also contain biochanin A and formononetin, which are precursors of genistein and daidzein, respectively [14]. The metabolites of daidzein include dihydrodaidzein, tetrahydrodaidzein, *O*-desmethylangolensin, and equol (4′,7-isoflavandiol) and these have been detected in human urine (Fig. 2) [17].

3.3 Dietary intake of soy products and isoflavones and prostate cancer risk

Evidence from epidemiological studies on the association of soy, isoflavones and the prostate cancer risk is still limited. Five cohort studies and eleven case-control studies met the selection criteria and were included in this review. A cohort study in the USA [18] with 225 incident cases of prostate cancer in 12 395 California seventh-day adventist men showed frequent consumption (more than once a day) of soymilk was associated with 70% reduction of the risk of prostate cancer (RR = 0.3, 95% confidence interval (CI) 0.1 – 0.9, P for linear trend = 0.02). Another population-based prospective study recruited 43 509 Japanese men aged 45 – 74 years and followed them up for 10 years (1995 through 2004). A validated questionnaire, which included 147 food items was used to investigate the effect of isoflavones intake and the risk of prostate cancer [19]. A total of 307 men were newly diagnosed with prostate cancer during the follow up, of which 74 cases were advanced and 220 cases were organ localized. Intakes of genistein, daidzein, miso soup (a traditional Japanese food made from slowly fermented soybeans), and soy food were not associated with prostate cancer in total, but increased consumption of genistein decreased the risk of localized prostate cancer. These results were strengthened when analysis was restricted to men aged >60 years, in whom isoflavones and soy food were associated with a dose-dependent decrease in the risk of localized cancer, with RRs for men in the highest quartile of genistein, daidzein, and soy food consumption compared

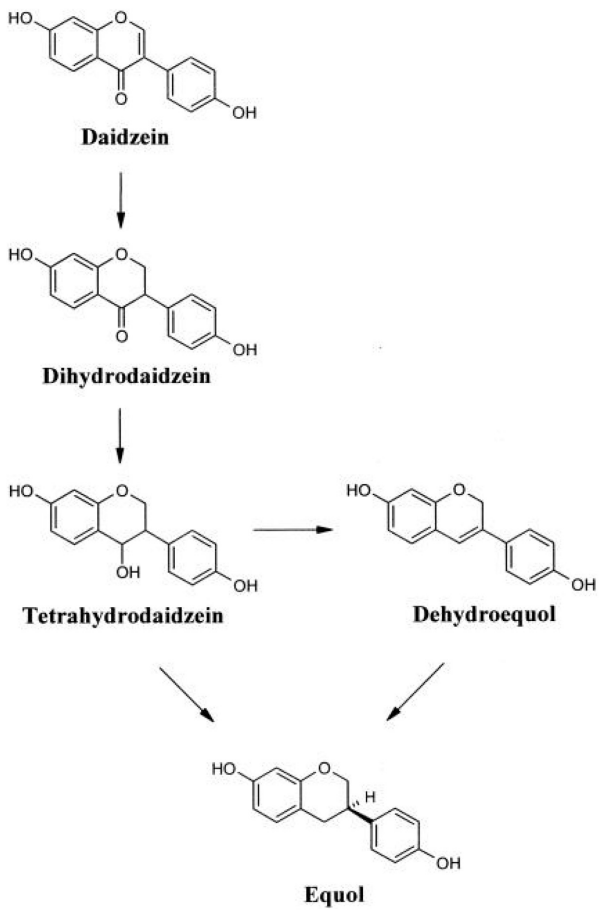


Figure 2. Proposed metabolic pathway leading to formation of equol from daidzein in a urine sample [17].

with the lowest of 0.52 (95% CI 0.30 – 0.90, P_{trend} = 0.03), 0.50 (95% CI 0.28 – 0.88, P_{trend} = 0.04), and 0.52 (95% CI 0.29 – 0.90, P_{trend} = 0.01), respectively. However, the relationship of miso soup consumption and advanced cancer is still unclear [20].

Table 2. Epidemiological studies on food intake of soy products and prostate cancer risk

Reference	Study type	Subjects	Study site	Food assessed	Intake comparison	RR/OR (95% CI)	P_{trend}	Adjusting factors
Kurahashi *et al.* 2007 [19]	Cohort	307 cases/ 43 509 cohorts	Japan	Soy food		>60 year:		Age, area, smoking, drinking frequency, marital status, BMI, fatty acid, dairy, vegetables, fruits
						Localized cancer:		
				Soy food	<46.6 g/day *vs.* 3107.4 g/day	0.52 (0.29–0.90)	0.010	
				Genistein	<13.2 mg/day *vs.* 332.8 mg/day	0.52 (0.30–0.90)	0.030	
				Daidzein	<8.5 mg/day *vs.* 320.4 mg/day	0.50 (0.28–0.88)	0.040	
				Miso soup	<110 mL/day *vs.* 3356 mL/day	0.65 (0.39–1.11)	0.220	
						Advanced cancer:		
				Soy food	<46.6 g/day *vs.* 3107.4 g/day	0.70 (0.25–1.95)	0.380	
				Genistein	<13.2 mg/day *vs.* 332.8 mg/day	1.03 (0.41–2.59)	0.870	
				Daidzein	<8.5 mg/day *vs.* 320.4 mg/day	1.49 (0.55–4.03)	0.750	
				Miso soup	<110 mL/day *vs.* 3356 mL/day	2.86 (1.01–8.11)	0.070	
Allen *et al.* 2004 [32]	Cohort	196 cases/ 252 602 cohorts	Japan	Tofu	<2 times/wk *vs.* daily	0.88 (0.58–1.35)	0.510	Age, calendar period, city of residence, radiation dose, education
				Miso soup	<2 times/wk *vs.* daily	0.94 (0.67–1.33)	0.640	
				Total soy	Low *vs.* high	0.79 (0.53–1.18)	0.230	
Nomura *et al.* 2004 [27]	Cohort	222 cases/ 5877 cohorts, Japanese Americans	Hawaii	Tofu	0 g/wk *vs.* >240 g/wk	0.82 (0.54–1.23)	0.760	Age, smoking, alcohol, total calories, arm muscle area, BMI
Jacobsen *et al.* 1998 [18]	Cohort	225 cases/ 12 395 cohorts	USA	Soymilk	0 *vs.* >1 time/day	0.3 (0.1–0.9)	0.020	Age, BMI, Coffee, whole fat milk, eggs, citrus, age at first marriage
Severson *et al.* 1989 [31]	Cohort	174 cases/ 7999 cohorts, Japanese Americans	Hawaii	Tofu	≤1 time/wk *vs.* 35 time/wk	0.35 (0.08–1.43)	0.054	N/A
Heald *et al.* 2007 [26]	Case-control	433 cases, 483 controls	UK	Soy food	No *vs.* yes	0.52 (0.30–0.91)	0.340	Age, energy, family history, Carstairs Deprivation index, smoking, EI:BMR ratio
Nagata *et al.* 2007 [60]	Hospital-based case-control	200 cases, 200 controls	Japan	Genistein	<1.1 mg/day *vs.* 32.5 mg/day	0.58 (0.34–0.97)	0.040	Smoking, energy intake
						0.68 (0.39–1.20)[a)]	0.190[a)]	
				Daidzein	<0.8 mg/day *vs.* 31.9 mg/day	0.55 (0.32–0.93)	0.020	
						0.64 (0.36–1.17)[a)]	0.120[a)]	
Sonoda *et al.* 2004 [28]	Hospital-based case-control	140 cases, 140 controls	Japan	Tofu	≥19.7 g/day *vs.* 396.4 g/day	0.47 (0.20–1.08)	0.160	Smoking, energy intake
				All soy products	≤77.0 g/day *vs.* 3187.2 g/day	0.53 (0.24–1.14)	0.110	
Jian *et al.* 2004 [33]	Hospital-based case-control	130 cases, 274 controls	China	Fermented soy products	0 *vs.* >4.0 g/day	2.02 (1.40–3.87)	0.003	Age, physical activity, locality of residence, education, income, marital status, family history, fresh vegetables and fruits, tea
Lee *et al.* 2003 [21]	Case-control	133 cases, 265 controls	China	Soy foods	<27.5 g/day *vs.* >111.8 g/day	0.51 (0.28–0.95)	0.061	Age, calorie
				Tofu	<14.3 g/day *vs.* >34.5 g/day	0.58 (0.35–0.96)	0.032	
				Genistein	<17.9 mg/day *vs.* >62 mg/day	0.53 (0.29–0.97)	0.058	
				Daidzein	<10.0 mg/day *vs.* 36.3 mg/day	0.56 (0.31–1.04)	0.116	

Kolonel *et al.* 2000 [22]	Multicenter case-control	1619 cases, 1618 controls, African-American, white, Japanese, and Chinese men	Hawaii, San Francisco, Los Angeles, British Columbia and Ontario	Soyfoods All legumes All legumes	0 *vs.* >39.4 g/day ≤10 g/day *vs.* >81 g/day Low *vs.* high	Total: 0.62 (0.44 – 0.89) 0.62 (0.49 – 0.80) African-American 0.65 (0.47 – 0.92) Chinese: 0.62 (0.38 – 1.01) White: 0.90 (0.64 – 1.26) Japanese: 0.78 (0.48 – 1.26)	 0.060 0.0002 0.020 0.040 0.520 0.130	Age, geographic location, education, calories, and when indicated, ethnicity
Jain *et al.* 1999 [24]	Population-based case-control	617 cases, 636 controls	Canada	Beans/lentils/ nuts	<3.6 g/day *vs.* >30.7 g/day	0.69 (0.53 – 0.91)	0.030	Age, energy intake, vasectomy, smoke, marital status, study area, BMI, education, vitamin supplements, grains, fruit, vegetables, total plants, carotenoids, *etc.*
Strom *et al.* 1999 [23]	Case-control	83 cases, 107 controls	USA	Genistein Daidzein Formononetin Biochanin A Coumestrol	19.8 μg/day *vs.* 29.7 μg/day[b] 14.2 μg/day *vs.* 22.8 μg/day 2.1 μg/day *vs.* 2.0 μg/day 57.1 μg/day *vs.* 61.6 μg/day 44.9 μg/day *vs.* 67.5 mg/day	0.71 (0.39 – 1.30) 0.57 (0.31 – 1.05) 0.99 (0.54 – 1.81) 0.92 (0.50 – 1.70) 0.48 (0.25 – 0.94)	0.260 0.070 0.980 0.790 0.030	Age, family history of prostate cancer, alcohol, calorie
Villeneuve *et al.* 1999 [29]	Population-based case-control	1623 cases, 1623 controls	Canada	Tofu, Soybean	0 *vs.* some	0.80 (0.60 – 1.10)	0.290	Age, residence, race, smoking, BMI, rice and pasta, coffee, grains and cereals, alcohol, fruit, tofu, meat, income, family history
Sung *et al.* 1999 [30]	Hospital-based case-control	90 cases, 180 controls	Taiwan	Soymilk	No *vs.* yes	0.95 (0.45 – 2.00)	N/A	N/A
Key *et al.* 1997 [25]	Population-based case-control	328 cases, 328 controls	UK	Baked beans garden peas	<1/m *vs.* ≥2/wk ≤3/m *vs.* ≥5/wk	0.57 (0.34 – 0.95) 0.35 (0.13 – 0.91)	N/A	N/A

N/A, not available.
a) Plus PUFA
b) Case *vs.* control, median

A case-control study in China showed an overall reduced risk of prostate cancer associated with consumption of soy foods and isoflavones [21]. In this study, 133 cases and 265 age- and residential community-matched controls from 12 cities were recruited. Results showed that the age- and total calorie-adjusted OR of prostate cancer risk was 0.58 (95% CI 0.35–0.96, $P_{trend} = 0.032$) comparing the highest tertile of tofu intake to the lowest tertile. There were also statistically significant associations of intake of soy foods (OR 0.51; 95% CI 0.28–0.95, $P_{trend} = 0.061$) and genistein (OR, 0.53; 95% CI, 0.29–0.97, $P_{trend} = 0.058$) but not daidzein (OR, 0.56; 95% CI, 0.31–1.04, $P_{trend} = 0.116$). A multiethnic case-control study carried out in Hawaii, San Francisco, and Los Angeles in the USA, and British Columbia and Ontario in Canada [22] revealed similar results. In this study, 1619 cases were diagnosed during 1987–1991 and were compared to 1618 controls of African-American, white, Japanese, and Chinese men. Controls were frequency-matched to cases on ethnicity, age, and region of residence of the case, in a ratio of approximately 1:1. ORs were estimated using logistic regression, adjusting for age, geographic location, education, calories, and when indicated, ethnicity. Intake of soy foods was inversely related to prostate cancer (OR, 0.62, 95% CI, 0.44–0.89). Results were similar when restricted to prostate-specific antigen-normal controls. While in advanced cases, no statistical significant protective effect was observed with high consumption of legumes (OR, 0.74, 95% CI, 0.52–1.06). Findings were generally consistent across ethnic groups. However, while the African-American and Chinese subgroups showed an inverse relationship between "all legumes consumption" and prostate cancer risk ($p < 0.05$), no significant inverse relationship was observed in whites and Japanese subgroup (see Table 2). These results suggest that legumes (not limited to soy products) may protect against prostate cancer and the extent of this effect may be different among various ethnic groups. A further four case-control studies from USA, Canada and UK showed similar results with a protective effect of consuming legumes (beans, lentils, garden peas, *etc.*) against prostate cancer [23–26].

On the other hand, some studies both in Western countries and Asian countries or regions did not find a statistical significant relationship between soybean milk, legumes intake and prostate cancer risk [23, 27–32]. In an early cohort study [31] among 7999 men of Japanese ancestry who were first examined between 1965 and 1968 and then followed through to 1986, 174 incident cases of prostate cancer were recorded. Increased consumption of tofu did not show statistical significant association with the risk of prostate cancer (RR = 0.35, 95% CI = 0.08–1.43). Our case-control study on Chinese men (130 cases and 274 controls) showed a weak positive association between consumption of fermented soy products and the risk of the prostate cancer [33]. A summary of epidemiological studies on food intake of soy products and prostate cancer risk is listed in Table 2. The conflicting findings from different epidemiological studies may partly attribute to improper study design such as small sample size, lake of differentiation of cancer stages, separate analysis for the effect of various types of soybean products, and diffeerent methods in measuring the quantity of soybean consumption. Poor quality data, such as low response rate and influence of prostate specific antigen screening on prostate cancer risk should also be considered.

3.4 Isoflavonoids concentration in biological specimens and the risk of prostate cancer

There is evidence that Asian people who habitually consume legumes and soybeans have higher plasma, urine, and prostatic fluid concentrations of isoflavonoids, including a higher equol-producer prevalence [34–37]. However, direct evidence of a causal relationship between the concentration of isoflavones in biological materials of prostate cancer patients and prostate cancer risk is limited and far from conclusive. Recently, there were three case-control studies measured serum levels of isoflavonoids in Japanese who consume their traditional food (see Table 3). One hospital-based case-control study [38] analyzed the serum levels of genistein, daidzein, and equol in 253 subjects (141 prostate cancer patients and 112 cancer-free controls). The results showed that the serum concentrations of isoflavones for both inpatients and outpatients with prostate cancer were higher than the controls; and the serum isoflavones levels were higher in outpatients than that in hospital patients. Daidzein metabolizers (producers) were significantly more common in the control group, and the poorly differentiated cancer case group included a significantly lower percentage of daidzein metabolizers. The serum concentrations of genistein and daidzein in subjects <70 years of age were significantly lower than subjects ≥ 70 years old. It is interesting that the cases had higher level of serum isoflavones than that of the controls, and the older age cases had higher level of serum isoflavones than younger cases. The question arises as to whether this was due to a change in dietary habits after diagnosis or whether it reflects a general change in the eating habits of Japanese of different age groups. The same research team [39] conducted a multicountry study in 2004 with 295 Japanese (133 patients and 162 controls), 122 Korean residents (case: control = 1:1) and 45 US residents (24 patients and 21 controls) of unconfirmed race. The percentage of people who can produce equol was 29% among cases and 46% among controls in Japan ($P = 0.004$), 30% and 59% in Korea ($P = 0.001$), and 17 and 14% in America ($P = 0.862$), respectively. Another nested case-control study (52 cases and 151 controls) in a community-based cohort ($n = 14\,105$) showed no significant differences in serum genistein and daidzein levels and the risk of the cancer, but higher serum equol levels were related to the lower risk of the cancer (OR = 0.39, 95% CI;

Table 3. Isoflavonoids concentrations in biological specimens of different ethnic groups

Reference	Study type	Subjects (male)	Age	Food control	No. of peoples	Daidzein	Equol
Ozasa *et al.* 2004 [40]	Case control	Japanese	69/69[a)]	N/A	52/151[a)]	Serum (nM), mean (P_{25}, P_{75}) 122 (72.1, 244.5)/139 (64.1,320.1)[a)]	Serum (nM), mean (P_{25}, P_{75}) 33.6 (14.0, 78.0)/55.4 (28.6, 145.9)[a)]
Akaza *et al.* 2004 [39]	Case control			Fasting		Blood (ng/mL), mean	Equol producer (%)
		Japanese	68/67[a)]		133/162[a)]	25.6/24.4[a)]	29/46[a)]
		Korean	70/64[a)]		61/61[a)]	29.9/30.3[a)]	30/59[a)]
		American	63/60[a)]		24/21[a)]	3.0/3.0[a)]	17/14[a)]
Akaza *et al.* 2002 [38]	Case control	Japanese		Fasting		Serum (ng/mL), median (range)	Serum (ng/mL), medium (range)
			69/67[a)]		141/112[a)]	35.7 (0.8 – 607)/21.5 (0.5 – 424)[a)]	16.0 (0.5 – 197)/5.2 (0.6 – 905)[a)]
						<70: 31.4/21.6[a)] ≥70: 49.3/19.3[a)]	Equol producer (%) 40/50[a)]
Morton *et al.* 2002 [37]	Cross-section	Healthy				Serum (nmol/L), median (range)	Serum (nmol/L), median (range)
		Japanese	64	No	102	148.5 (2.8 – 2,273)	31.7 (0 – 1,922)
		British	58		43	14.1 (0.9 – 99.6)	0.0 (0 – 6.3)
Morton *et al.* 1997 [34]	Multicenter, clinical trial					Plasma (ng/mL), mean (range)	Plasma (ng/mL), mean (range)
		Chinese	59	No	53	31.3 (0.7 – 433)	3.8 (0 – 120)
		Portuguese	55		50	1.3 (0 – 8.4)	0.4 (0 – 3.8)
		British	58		36	8.2 (1.2 – 36)	0.6 (0.1 – 9.5)
						Prostate fluid (ng/mL)	Prostate fluid (ng/mL)
		Chinese			20	70.0 (0.9 – 532)	171.6 (0 – 3270)
		Portuguese			22	4.6 (0 – 21.5)	1.7 (0 – 6.9)
		British			17	11.3 (0 – 62)	0.5 (0.5.1)
Adlercreutz *et al.* 1991 [35].	Cross-section					Urine (μmol/day), mean ± SD (geometric mean)	Urine (μmol/day), mean ± SD (geometric mean)
		Healthy Japanese	50		9	2.2 ± 2.0 (1.45)	3.0 ± 4.6 (0.54)

a) Case/control.

0.15, 0.89, P trend = 0.053) [40]. However these limited findings represent current legumes and soybean consumption by the subjects in the study rather than their previous habitual consumption. Summarized results in Table 3 indicate that the ability to metabolize daidzein to equol is different in various ethnic populations. It seems that as a metabolite of daidzein, equol or some unknown factor is involved in the biology of prostate cancer.

3.5 Laboratory studies on isoflavones and their anticancer effects

Genistein is a major component of soybean isoflavone and has multiple functions resulting in antitumor effects. There are increasing studies on the benefit effect from genistein. *In vitro* studies using prostate cancer cell lines have revealed that genistein may affect the expression of a large number of genes that are related to the control of cell survival and physiologic behaviors [41, 42], directly inhibit the growth of prostate cancer cells or through inducing apoptosis by inhibiting nuclear factor κB and signaling pathways [43, 44]. Genistein is a potent inhibitor of protein – tyrosine kinase, which may attenuate the growth of cancer cells and decrease the level of oxidative DNA damage [45 – 47]. Endoglin is a component of the transforming growth factor-β receptor complex abundantly expressed at the surface of endothelial cells. Endoglin is identified as an important suppressor of human prostate cancer cell motility, and its expression is lost during prostate cancer progression. A recent study in the US showed that genistein can activate activin like kinase receptor-2-small mothers against decapentaplegic homolog one endoglin-associated signaling to induce reversion of endoglin-deficient cells to a low motility, endoglin-replete phenotype. Thus, genistein will enhance the ability of endoglin in suppression of the motility of prostate cancer cell [48]. Moreover, genistein is also a potent inhibitor of angiogenesis and metastasis. It can effectively inhibit cell invasion by inhibiting transforming growth factor β-mediated phosphorylation of the p38 mitogen-activated protein kinase-activated protein kinase 2 and the 27 kDa heat shock protein [49].

Animal experiments have also shown that dietary concentrations of genistein can inhibit metastasis of prostate cancer [50]. Lifetime consumption of isolate/isoflavones

has prevented spontaneous development of metastasizing adenocarcinoma in Lobund–Wistar rat [51, 52]. Dietary genistein can also suppress the development of advanced prostate cancer in castrated TRAMP mice [53]. However, no available reports on intervention studies using both natural soy products and isoflavonoids that may distinguish the protective effect between the two.

In addition, consumption of soy foods is thought to contribute to prostate cancer prevention as a result of the hormonal properties of soy isoflavones, either through altered endogenous circulating or hormone-receptor signaling [54]. One small scale intervention study on circulating hormone profiles and androgen receptor (AR) expression patterns in men who had high-grade prostatic intraepithelial neoplasia ($n = 50$) and/or atypical small acinar proliferation ($n = 14$), or low-grade prostate cancer ($n = 5$) showed although AR expression in the prostate is suppressed by soy protein isolate consumption, none of the results were influenced by equol excretion status [54].

Although there is growing evidence for the beneficial action of isoflavonoids on multiple cancer-related biological pathways (carcinogen bioactivation, cell-signaling, cell cycle regulation, angiogenesis, oxidative stress, and inflammation), [52, 55–58] whether these observed protective effects are caused by the presence of dietary isoflavonoids, or whether they are merely indicators of a healthy diet in general, has not been concluded [59].

In conclusion, *in vitro* and *in vivo* studies all suggest that genistein is a promising agent for cancer chemoprevention and/or treatment. Research on other isoflavones is relatively rare compared with genistein.

4 Concluding remarks

In recent decades, we have seen an accumulating body of evidence from laboratory studies supporting the notion that diets rich in isoflavones are associated with a lower risk of prostate cancer. Limited epidemiological studies have also provided promising results that increasing consumption of diet rich in soy products and isoflavones may result in reduced risk of localized prostate cancer. More evidence from human studies is needed to confirm the effect of soy and isoflavones on advanced cancer. Limited human studies indicate that the protective effect in daidzein metabolizers is more evident than that in nonmetabolizers and the ethnic difference in daidzein metabolism may partly explain the variations of prostate cancer incidence between ethnic groups. Because the evidence suggesting legumes, including soy and soy products, protect against prostate cancer is limited and inconsistent [1], well designed large scale epidemiological studies among various countries to compare the incidence on daidzein metabolizers are needed and such studies are more important than merely comparing the concentration of various kinds of isoflavones. Studies on various soy products are also necessary to answer the questions whether preserved soy products provide similar protective effect on prostate cancer than fresh products, whether other isoflavones have similar effect as genistein on advanced cancer or whether soy products as food provide more beneficial effect than isoflavone supplements.

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