Chapter 12

Soybean and Prostate Cancer

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Additional information is available at the end of the chapter

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Part I: Consumption of Soybean and the incidence of Prostate Cancer in East and West

Prostate cancer is the most frequently diagnosed malignancy in men all over the world. The investigation from International Agency for Research on Cancer in World Healthy Organization of United Nations reported the data of 899, 000 new cases of prostate cancer in 2008, accounted for 13.6% of the total cancer cases. The investigation discovered the large difference of the incidence and the mortality of prostate cancer between in West and in East (Figure 1). In Western countries, the incidences and mortalities are significantly high. For example, the cases from Australia, Northern America or Europe, occupied nearly three-quarters of all the globe prostate cancer patients. In contrast, the incidences and mortalities in Asia are quite low, less than one tenth of that in Europe, the US or Australia of the West, especially in the South-Central Asia, showing the lowest incidence and mortality [1].

The significant difference of the incidences of prostate cancer addressed several important questions.

1. Why do Asian men have a much lower incidence of prostate cancer compared to men from the Western countries (the US and Europe)? Latent or clinically insignificant cancer of the prostate is found at autopsy at approximately the same rate in men from Asian countries as those from the USA (approximately 30% of men aged over 50 years), but there are large differences in the clinical incidence and mortality. Is there a strong possibility that diet and nutrition play a prominent role in accelerating or inhibiting the process by which clinically significant prostate cancer develops?

2. Is the fact that the hormone-dependent cancers of the prostate and breast show the same incidence and lifetime risk (the correlation r is 0.81 in 21 countries) related to diet?

3. East Asian countries, including Chinese and Japanese men, have the lowest incidence of prostate cancer in the world. But why, when Japanese men from those countries migrate to the North America, does their risk of developing prostate cancer increase 10-fold compared to their counterparts in Japan or China?

4. Although it is relatively rare in East, an increase in the incidence of prostate cancer has been reported in China, where the life style especially the diet structure is changing followed with the developed economy in recent years. What factors can account for the conspicuous increase?

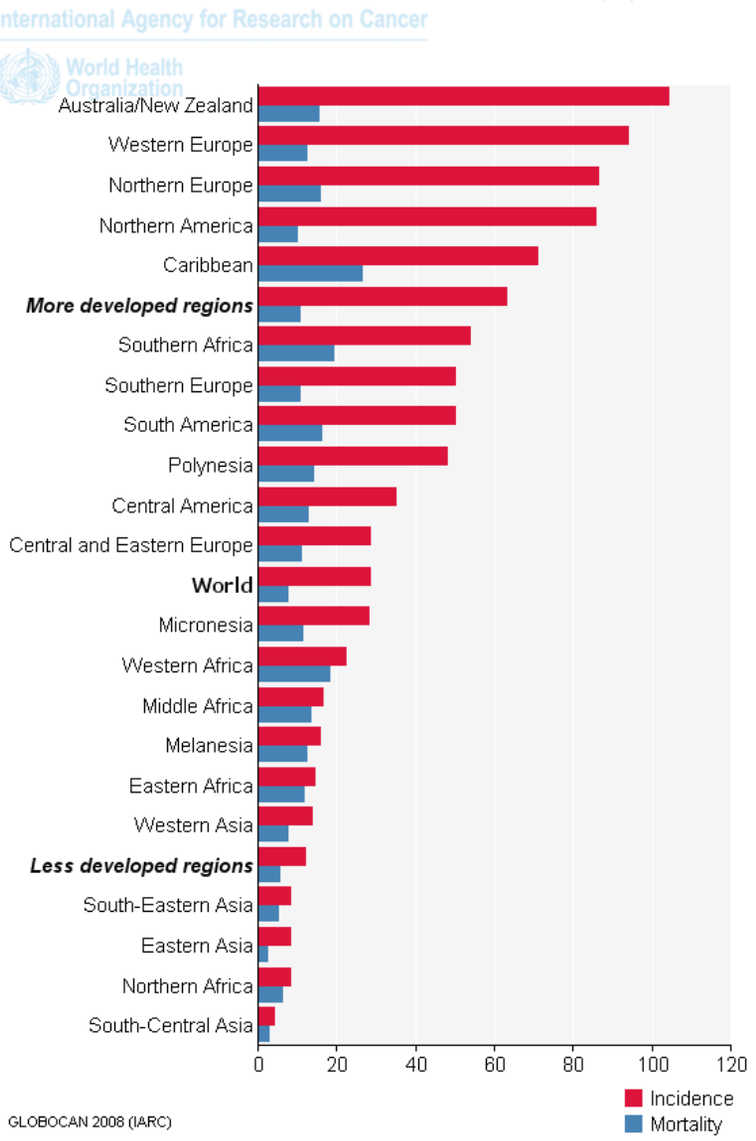

Figure 1. The incidence and mortality of Prostate cancer in the world, 2008(from International Agency for Research on Cancer)

Those questions highlight the critical roles of environmental dietary factors in the different risks of prostate cancer between East and West. Many epidemiological studies suggest that

the different dietary, most probably one kind of traditional food in the East countries, soybean, may become a dominant reason for the protective effects against prostate cancer [2].

Soybean, recognized as a complete protein food, is a species of legume and an annual plant in Asia. As being a traditional food in Asia, the history of soybean in Asia is very long, more than 5000 years and even before written records. Soybean can be made to a large body of kinds of foods by fermented or non-fermented process. Typical soy foods include soy milk, bean curd and tofu skin which are non-fermented soy foods as well as miso sauce, natto and soy sauce which belong to fermented soy foods. Not only fermented soybean foods, but also non-fermented soybean products are very essential dietary ingredient for Asian people, especially Chinese, Japanese and Koreans. Some Asians often have and their fermented or non-fermented products almost everyday. Japanese nearly had the soy food daily by ingestion of miso sauce and Chinese approximately had them more than 100 grams per day.

The history of soybean used in western countries is quite short, compared to that in Asia. Soybean was introduced into America, Australia and New Zealand about in 17th century and into Canada in 1831 as a sauce named "A new dozen India Soy". Most westerners hardly consume soy foods in the diet, although soybean and its products are used largely in some other ways, for example soybean oil could be made into bio-diesel in the United States. However Soy food consumption in the western countries are quite low. Soy foods have been consumed for centuries in Asian countries Japanese nearly had the soy food daily by ingestion of miso sauce and Chinese approximately had them by Tofu, soy milk and tofu skin.. The mean daily intakes of soy protein are approximately 30 grams in Japan, 20 grams in Korea, 7 grams g in Hong Kong, and 8 grams but more than 100 grams per day in some area in China [3]. While the average daily intake in the United States is less than 1 gram [4].

Country	Prostate cancer mortality	Total energy	Fish energy	Soy energy	Animal energy
Australia	**29.59**	3055	22	**0**	1019
Austria	**31.23**	3575	15	**0**	1233
Canada	**29.20**	3340	29	**0**	1297
France	**31.43**	3529	34	**0**	1343
Italy	**22.57**	3688	25	**0**	913
USA	**32.19**	3641	23	**1**	1316
Hong Kong	**5.44**	2771	89	**36**	834
Japan	**5.87**	2852	195	**93**	590
Korea	**0.90**	3056	67	**94**	269
Singapore	**7.47**	3165	63	**29**	689
Thailand	**0.53**	2330	37	**18**	152

Table 1. Prostate cancer and amount of soy food consumption in East and West, 1998 (from JNCI 1998; 90: 1637-1647)

For clear comparison of soybean in the Asian and the western diet, a table published in JNCI (Table 1), clearly clarified Prostate cancer and amount of soy food consumption in East and West. In Asian regions, the soybean energy is 36 in Hong Kong, 29 in Singapore and 18 in Thailand; and for much more dramatically difference, the soybean energy is 93 in Japanese, and 94 in Korean diet [5]. In contrast, in western countries of Australia, Austria, Canada, France, or Italia, the energy from soybean in daily dietary was zero, even in USA, the soy energy is only 1. This indicates that soybean is the dominantly different diet factor between the Eastern countries and the Western countries.

Interestingly the dramatically increased prostate cancer mortality in western countries, combined together with almost no soybean energy consumption, compare with very low mortality in Asia (only 1/60 to 1/6 of that in West), combined with high soybean energy consumption. This provided the important evidence for the consumption of soybean related to the lower risk of prostate cancer mortality. Even another point of the higher animal energy consumption in western diet, it is not that dominant as the difference of soy food.

Soy food	Study site	Finding	Study type	OR/RR	P trend	Reference
Soy food	Japan	protection	cohort	0.52(0.29–0.90)	0.010	Kurahashi 2007
Miso soup				0.65(0.39–1.11)	0.220	
Soymilk	USA	protection	cohort	0.30(0.1 – 0.9)	0.020	Jacobsen 1998
Tofu	Hawaii	protection	cohort	0.35(0.08–1.43)	0.054	Severson 1989
Soy food	UK	protection	case-control	0.52(0.30–0.91)	0.340	Heald 2007
Tofu	Japan	protection	case-control	0.47(0.20–1.08)	0.160	
All soy products				0.53(0.24–1.14)	0.110	Sonoda 2004
Soyfoods	China	protection	case-control	0.51(0.28–0.95)	0.061	
Tofu				0.58(0.35–0.96)	0.032	Lee 2003
Soyfoods	Hawaii,San Francisco,	protection	case-control	0.62(0.44–0.89)	0.060	
All legumes	Los Angeles, British Columbia and Ontario			0.62(0.49–0.80)	0.0002	Kolonel 2000
Beans/lentils/ nuts	Canada	protection	case-control	0.69(0.53–0.91)	0.030	Jain 1999
Tofu, Soybean	Canada	protection	case-control	0.80(0.60–1.10)	0.290	Villeneuve 1999
Soybean foods	China	protection	case-control	0.29(0.11-0.79)	0.02	Li 2008
Baked beans	UK	protection	case-control	0.57(0.34–0.95)	N/A	Key 1997
Garden peas	UK			0.35(0.13–0.91)	N/A	

Table 2. N/A:no adequate dataEpidemiological studies on food intake of soy products and prostate caner risk(most data summrized from Mol Nutr Food Res. 2009; 53: 217-226)

Most epidemiological studies have suggested that the consumption of soy food is associated with a reduction in prostate cancer risk in humans. Eight case-control studies and three cohort studies have reported the protective effect of soy food, with odds ratios or relative risks ranging from 0.3 to 0.80, including in China and Japan, where people consume more soybean food, tofu, soymilk and natto. Here the epidemiological data are summarized in Table 2 [6].

Some cohort studies provided the convincing data on this issue. A population based prospective study recruited 43 509 Japanese men aged 45–74 years and followed them up for 10 years (1995 through 2004). For men aged 60 years, in whom soy food were associated with a dose-dependent decrease in the risk of localized cancer, with RRs for men in the highest quartile of soy food consumption compared with the lowest obtained a protective OR of 0.52 (95% confidence interval (CI) 0.29–0.90, P trend = 0.01) [7]. A cohort study in the USA with 225 incident cases of prostate cancer in 12395 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%CI 0.1–0.9, P trend = 0.02) [8]. In an early cohort study 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) [9].

Much more case-control studies provided more evidence for the reduced risk of prostate cancer associated with consumption of soy foods. First we concentrate some case-control studies conducted in men living in China. Our group carried out a population-based case-control study in China to investigate the possible correlation factors for prostate cancer, 28 cases from 3940 men over 50 years old with prostate-specific antigen screening in Changchun city in China, matched them with controls of low prostate-specific antigen value (< 4.1 ng/mL) by 1: 10 according to age and place of employment. In all ten food items, the consumption of soybeans was demonstrated the only factor to decrease the risk of prostate cancer. Men who consumed the soybean product of Tofu and soymilk more than once per day had a multivariate OR of 0.29 (95% CI, 0.11–0.79) compared with men who consumed soybean products less than once per week. The P for trend was 0.02. There was no significant difference for any other dairy food (2). Another case-control study in China of 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= 0.032) in the highest tertile of Tofu intake comparing 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 = 0.061) [10].

The case-control studies also provide the similar evidence for that the soy intake protect against prostate cancer. A case-control study of diet and prostate cancer in Japan demonstrated the possible protective effect of traditional Japanese soybean die plays a preventive role against prostate cancer in four geographical areas (Ibaraki, Fukuoka, Nara, and Hokkaido) of Japan. All 140 cases and 140 age -matched hospital controls were analyzed to confirm the consumption of fish and natto showed significantly decreasing linear trends for risk,

with RR of 0.53 (95% CI, 0.24-1.14) ($P < 0.05$) for all soybean products, 0.47 (95% CI, 0.20-1.08) for tofu, and 0.25 (95% CI, 0.05-1.24) for natto [11].

Not only has the case-control research conducted in Asian men supported the hypothesis that the rich soybean products may protect against prostate cancer but many case-control studies conducted in western countries also provid the epidemiological evidence for the protective effects of soy food against prostate cancer. A multiethnic case-control study carried out in Hawaii, San Francisco, and Los Angeles in the USA, and British Columbia and Ontario in Canada, 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. Intake of soy foods was inversely related to prostate cancer with OR of 0.62 (95% CI, 0.44–0.89). Results were similar when restricted to prostate-specific antigen normal controls [12]. 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. A case-control study in Canada for a total study population consisted of 617 incident cases of prostate cancer and 636 population controls from Ontario, Quebec, and British Columbia. To obtain a decreasing, statistically significant association was found with increasing intakes of beans/lentils/nuts (OR = 0.69, 95% CI, 0.53-0.91) [13]. Another population-based case-control study conducted in eight Canadian provinces. Risk estimates were generated by applying multivariate logistic regression methods to 1623 histologically confirmed prostate cancer cases and 1623 male controls aged 50-74 to obtained a OR 0.80 (95% CI, 0.60-1.10) of Tofu and Soybeans [14]. Not only soybean but also other legumes had the inverse relationship against prostate cancer. Oxford group in UK found the baked beans had an OR of 0.57 (95% CI, 0.34-0.95); and garden peas had an OR of 0.35 (95% CI, 0.13-0.91) [15]. And a population-based case-control study of diet, inherited susceptibility and prostate cancer was undertaken in Scotland investigated a total of 433 cases of Scottish men and 483 controls aged 50-74 years, indicates the theoretical scope for reducing the risk from prostate cancer, with the consumption of soy foods (adjusted OR 0.52, 95 % CI 0.30-0.91) [16].

All these data from both East and West, summarized in Table 2, provide the convincing epidemiological evidence that the higher intake of soy products is associated with a reduced risk of prostate cancer in human. Some experimental data in animal model also demonstrated the possible protective effects for Soybean food against prostate cancer. For example, Zhou group demonstrated that dietary soy products inhibit the experimental prostate tumor growth through a combination of direct effects on tumor cells and indirect effects on tumor neovasculature in mice, confirming that soy foods could act as a preventive factor against prostate cancer in animal models [17].

Prostate cancer has marked geographic variations between countries. The data from both western and eastern countries support the critical roles of soybean food in the protection of prostate cancer.

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Part II: Correlation between prostate cancer and soybean isoflavones from diet, serum epidemiological and laboratorial data

In recent decades, much evidence from epidemiological studies support the notion that frequent consumption of soybean foods, the most different diet between East and West, is beneficial for the protection against prostate cancer.

Soybeans are high in protein, for about 35% to 40% of the dry weight. They also contain 18% polyunsaturated fats, 30% carbohydrates, and some vitamins, minerals. They are the only legume that provides ample amounts of the essential omega-3 fatty acid alpha-linolenic acid.2 Soybeans are a rich source of isoflavones (or phytoestrogens), a subclass of flavonoids that bind to estrogen receptors (though not as strongly as estrogen). Isoflavones are also discovered in peanut, alfalfa; however, soybean contains the largest amounts of isoflavones in the nature. Soybeans and soy foods such as tofu, soymilk, and miso are the only significant dietary sources of these phytoestrogens. In soybeans, isoflavones bound to a sugar molecule as glycoside, and when soybean is fermented or digested, isoflavones could be released from the bounded sugar [18].

Table 3 summarized the relationship between isoflavones levels and soy protein content in a variety of soy-containing foods. The isoflavones in soymilk are lowest, 2.5mg per 100g soymilk, may because in the fluid soymilk, the nutrition of soybeans is dissolved in water and lower concentration of nutrition in soymilk, whereas isoflavones in soy flour are highest, 131.2 to 198.9mg per 100g. In tofu, a traditional soy food in Asia, the isoflavones are 27.9mg/100g. In the traditional and very important Japanese soy food, the isoflavones in miso are 42.6mg/100g. The isoflavones in natto are 20mg/100g. The information from Table 3 clearly provides the amounted isoflavones in some other soybean foods as well. In the most frequently diet, each gram of soy protein is associated with approximately 3.6 mg of isoflavones in Tofu, 3.7 mg of isoflavones in whole bean based soymilk [19].

As the special nutrition in soybean compared to other plants, the isoflavones have many health benefits, including protection against chronic diseases, menopausal symptoms, osteoporosis and breast cancer or prostate cancer [20]. The most effective soy isoflavones are well known as genistein and daidzein. Here, the relationship between each soybean isoflavones and prostate cancer would be further illustrated.

The epidemiological evidence for the association of soy isoflavones and the prostate cancer risk is still limited. Some epidemiological data, summarized in Table 4, evaluated the effects of soybean isoflavones on prostate cancer. To date, one study suggests a causal relationship between isoflavones and prostate cancer, but two cohorts and two case-control studies suggest that soy isoflavones, genistein and daidzein, have prophylactic effects on prostate cancer. In addition,, an accumulating body of evidence from laboratory studies in recent decades has suggested that diets rich in high concentration of isoflavones are associated with anti-tumor effects in prostate cancer.

	estimated protein (g/100 g)	total isoflavones (mg/100 g)	isoflavone (mg/g protein)
soy products			
soybean chips	54.2	35	0.6
soy links frozen raw	3.9	15	3.9
natto boiled fermented	46.4	20	0.4
tofu, silken, firm	7.8	27.9	3.6
tempeh	14.9	43.5	2.9
miso	12.5	42.6	3.4
soy cheese, Cheddar	7.2	28	3.9
soy cheese, mozarella	7.7	32	4.2
soy cheese, Parmesan	6.4	36	5.6
soy milks			
soy milk, isolate based, low isoflavone	3.3	2.5	0.7
soy milk, isolate based, high isoflavone	3.3	4.4	1.3
soy milk, whole bean based, low isoflavone	3.1	2.4	0.8
soy milk, whole bean based, high isoflavone	3.1	11.6	3.7
soy milk, entire bean	3.1	3.6	1.2
soy milk	3.5	9.7	2.8
soy protein materials			
soy protein isolate, aqueous extract, type 1	85	114	1.3
soy protein isolate, aqueous extract, type 2	85	78.7	0.9
soy protein isolate, aqueous extract, type 3	85	103.4	1.2
soy protein isolate, alcohol extract	85	81.9	1.0
soy protein concentrate, alcohol extract	65	12.5	0.2
soy flour, defatted	50	131.2	2.6
soy flour, full fat, raw	35	177.9	5.1
soy flour, full fat, roasted	39	198.9	5.1

Table 3. Relationship between isoflavone levels and soy protein content in a variety of soy-containing foodsfrom J. Agric. Food Chem. 2003; 51: 4146-4155

2.1. Genistein

Genistein, firstly isolated from Genista tinctoria in 1899, was abundant in soybean. Even though a serum case-control study suggested the promotion roles of genistein for the prostate cancer risk; most studies demonstrated its protective effects against prostate cancer. Two cohort studies and two case control studies demonstrated the significant protective roles of genistein against prostate cancer, with multivariate RRs (ORs) of 0.71, 0.52, 0.58 or 0.53, summarized in Table 4.

Phynoestrogen	Study site	Findings	Study type	OR/RR	P_{trend}	Reference
genistein						
	Europe	protection	cohort	0.71(0.53-0.96)	0.030	
	Japan	protection	cohort	0.52(0.30-0.90)	0.030	
	protection	case-control		0.58(0.34-0.97)	0.040	Nagata 2007
	protection	case-control		0.53(0.29-0.97)	0.058	Lee 2003
	Japan	promotion	serum case-control			Akaza 2002
daidzein						
	Japan	protection	cohort	0.50(0.28-0.88)	0.040	Kurahashi 2007
	Japan	protection	case-control	0.55(0.32-0.93)	0.020	Nagata 2007
	China	protection	case-control	0.56(0.31-1.04)	0.116	Lee 2003
	Japan	protection	serum case-control			Akaza 2002

Table 4. Effects of photoestrogens on cacinogenesis of prostate cancer in epidemiological or animals experimental data.

The population based prospective study recruited 43 509 Japanese men aged 45–74 years and followed them up for 10 years (1995 through 2004). All 147 food items in 220 cases with organ localized cancers was investigated the relationship of isoflavones intake and the risk of prostate cancer. The increased consumption of genistein was found associated with the decreased risk of localized prostate cancer. These results were strengthened when analysis was restricted to men aged more than 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 consumption compared with the lowest of 0.52 (95% CI 0.30–0.90, P trend = 0.03) [7].

Another Japanese group examined associations between nutritional and the prevalence of prostate cancer in a case-control study of Japanese men. Two hundred patients and 200 age-matched controls were selected from 3 geographic areas of Japan. Isoflavones and their aglycones (genistein and daidzein) were significantly associated with decreased risk, with the OR for genistein 0.58 (95% CI 0.34–0.97, P trend = 0.04), indicating that isoflavones might be an effective dietary protective factor against prostate cancer in Japanese men [21].

A case-control study in China showed an overall reduced risk of prostate cancer associated with consumption of soy foods and genistein. 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 genistein (OR, 0.53; 95% CI, 0.29–0.97, P trend = 0.058) [10].

Notably, a recent prospective investigation of plasma phytoestrogens and prostate cancer in the European also found that higher plasma concentrations of genistein were associated with lower risk of prostate cancer. They examined plasma concentrations of phyto-oestrogens in relation to risk for subsequent prostate cancer in a case-control study nested in the European Prospective Investigation into Cancer and Nutrition. Concentrations of isoflavones genistein, daidzein and equol, and that of lignans enterolactone and enterodiol, were measured in plasma samples for 950 prostate cancer cases and 1042 matched control participants. Relative risks (RRs) for prostate cancer in relation to plasma concentrations of these phyto-oestrogens were estimated by conditional logistic regression. Higher plasma concentrations of genistein were associated with lower risk of prostate cancer, the RR among men in the highest vs. the lowest fifth was 0.71 (95%CI 0.53-0.96, P trend=0.03). After adjustment for potential confounders, this RR was 0.74 (95% CI 0.54-1.00, P trend=0.05). No statistically significant associations were observed for circulating concentrations of daidzein, equol, enterolactone or enterodiol in relation to overall risk for prostate cancer [22].

Laboratory studies revealed that Genistein has multiple functions in the antitumor effects against prostate cancer, with the concentration as the prominent associated factor. In 2002, an Italy group declared that at low concentration, about 1~10μM, genistein would stimulate androgen-dependent prostate cancer cell line LNCaP growth, but when genistein was at high concentration, more than 100μM, it would result in cell apoptosis in prostate caner [23]. The conclusions above were supported by the research of another Gao's group, published in the journal of the Prostate in 2004 [24].

In vitro studies in several prostate cancer cell lines have revealed that genistein directly inhibit the growth of prostate cancer cells or through inducing apoptosis, affecting the expression of a large number of genes that are related to the control of cell survival and physiologic behaviors [25,26]. As tyrosine kinase inhibitor and topoisomerase inhibitor, genistein induces cancer cell apoptosis by upregulating the expression of cyclin-dependent kinase inhibitor p21 or inhibiting the activity of nuclear factor kappa B (NF-kB) signaling pathways [27, 28]. 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 [29-31]. Genistein also reported to enhance the ability of endoglin, a component of the transforming growth factor beta receptor complex, in suppression of the motility of prostate cancer cell [32]. 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 [33].

The anti-tumor effects of genistein are demonstrated in the animal models. Animal experiments have also shown that dietary concentrations of genistein can inhibit metastasis of prostate cancer [34]. Lifetime consumption of isolate/isoflavones has prevented spontaneous development of metastasizing adenocarcinoma in Lobund–Wistar rat [35, 36]. Dietary genistein can also suppress the development of advanced prostate cancer in castrated transgenic adenocarcinoma of mouse prostate (TRAMP) mice [37]. Some other result also indicated biphasic role for genistein in the regulation of prostate cancer growth and metastasis. A low

concentration of 500 nmol/L of genistein to 12-week-old TRAMP-FVB mice as evidenced by increased proliferation, invasion. But a pharmacologic dose (50 nmol/L) decreased proliferation, invasion, and MMP-9 activity (>2.0-fold) concomitant with osteopotin reduction [38]. With 250 mg genistein/kg diet in treatments (TRAMP) mice model, the most significant effect was seen in the TRAMP mice exposed to genistein throughout life (1-28 weeks) with a 50% decrease in poorly-differentiated cancerous lesions. In a separate experiment in castrated TRAMP mice, dietary genistein suppressed the development of advanced prostate cancer by 35% compared with controls. The data obtained in intact and castrated transgenic mice suggest that genistein may be a promising chemopreventive agent against androgen-dependent and independent prostate cancers [39]. This group further identified the associated signaling, and revealed that Genistein in the diet significantly inhibited the cell proliferation by down-regulating tyrosine kinase regulated proteins, EGFR, IGF-1R, and down-regulating the downstream mitogen-activated protein kinases, ERK-1 and ERK-2 in prostates in TRAMP mice [37].

Genistein is demonstrated to be synergy with other phyto-chemicals together to inhibit the growth of prostate cancer. For example, genistein and curcumin is reported could inhibit the growth of prostate cancer cells in a synergistic way. Genistein, together with DIM, was proved to repress the proliferation of androgen-dependent prostate cancer cell line LNCaP and androgen-independent prostate cancer cell line PC-3 [40]. Genistein, together with biochanin A, could also inhibit the growth of human prostate cancer cells [41]. Genistein is also reported acts as a radiosensitizer for prostate cancer both in vitro and in vivo inhibit metastasis of prostate cancer [34].

Based on the studies above, a conclusion is deduced that genistein showed protective effects against prostate cancer, in vivo and in vitro, at its high concentration.

2.2. Daidzein

Daidzein is another important soy isoflavone. Most of epidemiological studies prove that daidzein contributes to the reduction of prostate cancer risk and the prevention of prostate cancer. A cohort study and two case control studies demonstrated its significant preventive roles of daidzein for the prostate cancer prevention, with multivariate RRs (ORs) of 0.50, 0.55 or 0.56, summarized in Table 4.

Several studies indicated that daidzein might be an effective dietary protective factor against prostate cancer in Japanese men. One cohort study of the population based prospective study recruited 43 509 Japanese men aged 45–74 years mentioned above and followed them up for 10 years. From 147 food items in 220 cases with organ localized cancers was investigated and isoflavones intake was founded to be associated with the risk of prostate cancer. In men aged more than 60 years, RRs for men in the highest quartile of daidzein consumption compared with the lowest of 0.50 (95%CI 0.28-0.88, P trend = 0.04) [7]. Another Japanese group examined associations between nutritional and the prevalence of prostate cancer in a case-control study in Japanese men. Two hundred patients and 200 age-matched controls were selected from 3 geographic areas of Japan, demonstrated that daidzein

were significantly associated with decreased risk, with the OR 0.55 (95% CI 0.32–0.93, P trend = 0.02) for daidzein [21].

A case-control study in China showed an overall reduced risk of prostate cancer associated with consumption of soy daidzein. 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 even not statistically significant associations, but the protective trend for the intake of daidzein (OR, 0.56; 95% CI, 0.31–1.04, P trend = 0.116) [10].

Daidzein displays the modest protective effect against prostate cancer from the experimental data. Daidzein could act as a radiosensitizer against prostate cancer and an inhibitor of cell growth. Daidzein inhibited cell growth and synergized with radiation, affecting APE1/Ref-1, NF-kappaB and HIF-1alpha, but at lower levels than genistein or soy [42].

In addition, the protective effect on prostate cancer was strengthened after daidzein was combined with genistein, compared to individual one. The study from Oregon State University demonstrated daidzein and genistein could also induce cell apoptosis in benign prostate hyperplasia (BPH) cells at concentration of 25 μM. Soy extractions were indicated more effective as chemopreventive agents than genistein or daidzein. A combination of active soy-derived compounds is demonstrated more efficacious and safer as chemopreventive agents than individual compound. Soy extracts also increased Bax expression in PC3 cells [43]. Isoflavones exert their chemopreventive properties by affecting apoptosis signaling TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) pathways in prostate cancer LNCaP cells. The chemopreventive effects of soy foods on prostate cancer are associated with isoflavone-induced support of TRAIL-mediated apoptotic death [44].

Soy isoflavones, including daidzein and genistein, exert anticarcinogenic effects against prostate cancer, proposed that soy extracts, containing a mixture of soy isoflavones and other bioactive components, would be a more potent chemo-preventive agent than individual soy isoflavones.

Part III: The mechanisms of prevention effects of soybean phyto-estrogens against prostate cancer.

Isoflavones are the best-known phyto-estrogens, are a diverse group of naturally soy compounds, play important roles in prostate cancer inhibition. The consumptions of soy isoflavone are investigated to be an effective protection factor against certain diseases. And the products rich in isoflavones might protect against enlargement of the male prostate gland, slow prostate cancer growth and lead to prostate cancer cell death.

The chemical structure-based ligand and receptor binding is the most important primary step in generating downstream signal transduction. To reveal their mechanisms of prevention effects against prostate cancer, their specific structures for the receptor binding are

illustrated. Isoflavones are classified to phyto-estrogens, because their structures are similar to estradiol (17β-oestradiol), also could mimic estrogenic effect to bind to estrogen receptors. However, their structures are similar not only to estradiol, but also to dihydrotestosterone (DHT), the most important steroid hormone in male. DHT and 17β-oestradiol, endogenous steroid hormones, have a four-ringed carbon backbone, where as non-steroid hormone thyroxin has a quite different structure from them (Figure 2). The isoflavones of genistein and daidzein are two phyto-oestrogens found at very high levels in soy formula. Flavone, another group of phyto-estrogens, is found abundant in many plants. The structures of genistein, daidzein and flavone showed similar properties: a hydrophobic core and one or two terminal polar groups, similar to 17β-oestradiol or DHT (Figure 2), have the ability to cause estrogenic or/and anti-testosterone effects through the modulation of androgen receptor (AR) transactivation.

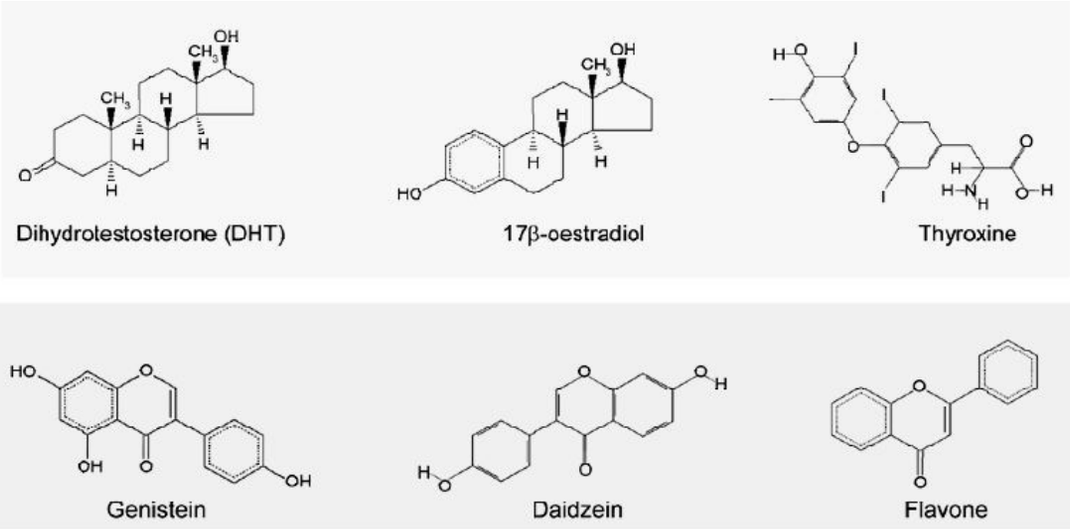

Figure 2. Molecular formulas of ligand compounds, two endogenous steroid hormones of dihydrotestosterone (DHT) and 17β-oestradiol, one endogenous non-steroidal hormone, thyroxin, and three phyto-estrogens of genistein, daidzein and flavone. from Asian J Androl. 2010; 12: 535-547

The normal development and maintenance of the prostate is dependent on androgen acting through the AR, which is driven by DHT plays a critical role in prostate cancer development and progression. AR expression is maintained throughout prostate cancer progression, and the majority of androgen-independent or hormone refractory prostate cancers with the overexpression or the mutation of AR. This progress may be affected by the soybean phyto-oestrogens, as mimic oestrogens, compete the same binding sites of AR that binds to DHT, further affect androgen-controlled AR mediated prostate cancer growth and development [45].

To reveal the mechanisms of these isoflavones for prostate cancer, our group adopted a computerized approach to examine the interaction of the human AR and isoflavone (genistein or daidzein), whereas the interaction of AR and flavone was set up as a positive control. Auto Dock method was adopted to summarize the roles of genistein, daidzein in AR activity regulation, further to evaluate the importance of isoflavones for the tumor repression

against prostate cancer. Auto Dock applies a half-flexible docking method, which permits small molecular conformation changes. Based on a complex 'lock-and-key model', it is an excellent method to reveal ligand–receptor binding. The result of computer stimulation from Auto Dock contains two parts, one is the binding site of a ligand docked in the receptor and the other is the binding affinity when a ligand is docked in the receptor.

The 3D spatial structure of AR-LBD was obtained from RCSB Protein Data Bank and its PDB ID is 2ama (676-919AA). The positive-control docking result showed that 17β-oestradiol fit the ligand-binding site of AR, at the same position in AR as its natural ligand, DHT. The negative control, thyroxine, showed a quite different binding position with external docking site (Figure 3A). Comparing the three endogenous ligands, thyroxine was expected to have the weakest binding to AR and the highest affinity energy, which we measured at -5.4 kcal mol^{-1}. Very strong binding to AR with lower affinity energies was expected in the two steroid hormones, with affinity energies of -11.2 kcal mol^{-1} for DHT and -10.7 kcal mol^{-1} for 17β-oestradiol (Figure 3B) [46].

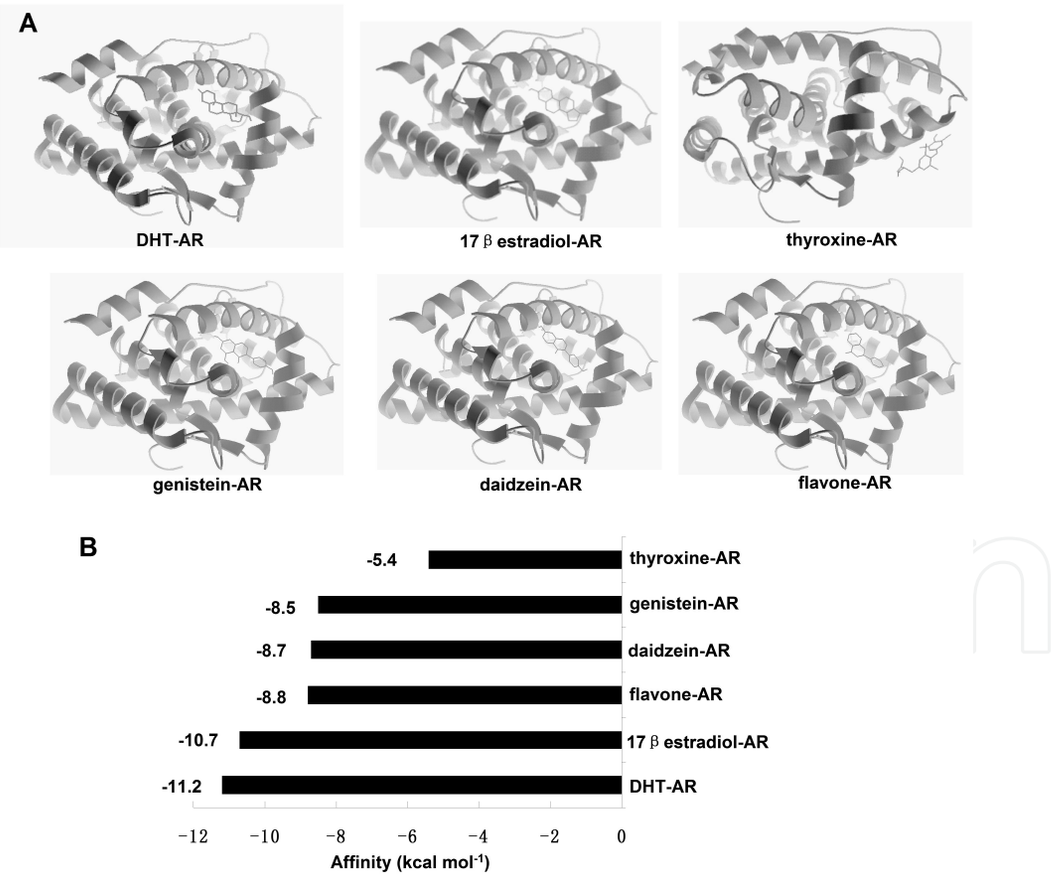

Figure 3. Auto docking analysis of endogenous hormones or phyto-estrogens binding to androgen receptor.(A) Positions of the steroid hormones of DHT or 17β-oestradiol, endogenous non-steroid hormone, thyroxin, phyto-estrogens of genistein, daidzein or flavone binding to androgen receptor.(B): The affinity energies of each ligand binding to androgen receptor. from Asian J Androl. 2010; 12: 535-547

Genistein and daidzein are abundant in soy formula and as healthy ingredient in soybean to protect against prostate cancer. To understand the role of the isoflavone compounds in prostate cancer, a computerized auto-dock system was adopted to examine the interactions between the human AR and phyto-oestrogens (genistein, daidzein, and flavone). As shown in Figure 3 genistein, daidzein and flavone fit in the middle region of the AR-LBD (Figure 3A), the same as DHT and 17β-estradiol. The affinities of them were expected to lie between the affinities of thyroxin and 17β-estradiol. Genistein and daidzein, soy isoflavones, showed affinity energies of -8.5 and -8.7 kcal mol^{-1}, respectively, which were very similar to the affinity energy of flavone of -8.8 kcal mol^{-1}. From that result, we concluded that the three (iso) flavones exhibit similar binding affinities to AR (Figure 3B). Considering their sharing of a binding site with estradiol, their affinities for AR and quantities potentially consumed in the diet, these phyto-estrogens could have significant effects on AR and AR-related cancers [46].

The phyto-estrogens (genistein, daidzein and flavone) can bind to AR in an Auto Dock model and can be regarded as androgenic effectors, suggesting important roles for them in AR-mediated cancers. Interestingly, all these phyto-estrogens are reported to be associated with prostate cancer, so we consider them AR-related phyto-estrogens. We summarized some recent data about the effects of them on AR-mediated transcriptional activity and on prostate tumorigenesis in Table 5. Genistein, daidzein and flavone, implicated as androgenic effectors in our research, indeed regulate AR-mediated PSA transcriptional activity. They have been demonstrated previously to either enhance AR-mediated transcriptional activity or inhibit DHT induced AR-mediated PSA activity. Moreover, isoflavones or soy beverage has already been shown in Phase II trials to decrease PSA levels in prostate cancer patients. It is noteworthy that two recent phase II trials showed that isoflavones or soy beverage can decrease PSA levels in prostate cancer patients, suggesting that androgen receptor target genes can be regulated by isoflavones or flavones [46].

Phynoestrogen	Findings	Study type	Reference
genistein	inhibition of R1881-induced AR mediated pPSA-luc activity	reporter assay	Davis 2002
	decrease AR binding to ARE	EMSA	
	inhibition of R1881-induced AR mediated pPSA-luc activity	reporter assay	Gao 2004
	enhancement of AR mediated pPSA/ARE/Probasin/ MMTV-luc		
daidzein	enhancement of AR (with ARA) mediated MMTV-luc	reporter assay	Chen 2007
flavone	inhibition of DHT-induced AR mediated pPSA-luc activity	reporter assay	Rosenberg 2002
soy food	decline of serum PSA	PhaseII trail	Kwan 2010 Pendleton 2008

Table 5. Effects of photoestrogens on AR mediated transcriptional activityfrom Asian J Androl. 2010; 12: 535-547

The mechanism of these phyto-estrogens against prostate cancer has been studied, some laboratory studies demonstrated that phyto-estrogens might not only mimic estrogenic activities but also interfere with other steroid hormones, for example DHT, the natural androgen in men. In human body, the activity of DHT binding with androgen receptor can be weaken in the presence of a large amount of these phyto-estrogens, genistein, daidzein and flavone.

The findings in Auto Dock interestingly demonstrate that phyto-estrogens are displayed the great binding abilities to AR, demonstrating their disrupt effects against DHT/AR binding as anti-androgenic effectors, supporting the epidemiological studies that soybean were the potential inhibitor for prostate cancer cell growth related to AR. Figure 4 illustrated clearly the mechanism of phyto-estrogens against prostate cancer. The different consumption of soy foods and the different concentrations of isoflavones possibly disrupt the endogenous DHT binding to AR in the prostate and thus inhibited DHT induced AR translocation and AR-mediated PSA transactivation, thus reduce prostate cancer risk. As the antagonists of androgen, phyto-estrogens are ale to inhibit the cell growth induced by androgen in prostate gland.

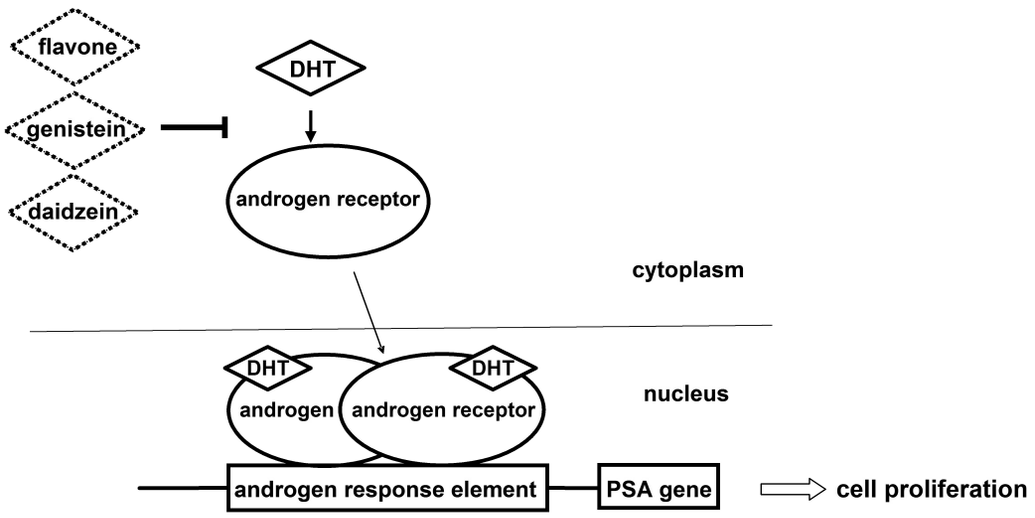

Figure 4. The mechanism of protective effect of genistein, daidzein or flavone against prostate cancer.

The reasons that Asian populations have lower rates of hormone-dependent cancers (breast, prostate) and lower incidences of menopausal symptoms and osteoporosis than Westerners are still need to be further revealed. However, the association of the large quantities of soy products consumption in Asian populations with the reduction in the risk of prostate cancer, provides a unique insight for the beneficial effects of soy foods. Soy food display completely different consumption between eastern and western populations. The geometric mean levels of plasma total isoflavonoids were demonstrated to be 7-10 times higher in Japanese men than in Finnish men. Asian immigrants living in Western nations also have increased risk of these maladies as they 'Westernize' their diets to include more protein and fat and reduce their soy intake. This provides a good explanation for much epidemiological data, indicating the significant protective effect of (iso) flavones for prostate cancer.

The much higher serum phyto-estrogen levels could hypothetically inhibit the growth of prostate cancer in Chinese and Japanese men, which may give a good explanation for the quite low incidence and mortality from prostate cancer in Japan or China. The novel important insights for soy food against prostate cancer need to be further illustrated. Soy-based food products are expected to introduce more to the western markets and to have more consumption in western daily diet.

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