Soy Food Consumption and the Risk of Prostate Cancer: A Meta-Analysis of Observational Epidemiological Studies

연세대학교 보건대학원

역 학 통 계 학 과

황 예 원

Soy Food Consumption and the Risk of Prostate Cancer: A Meta-Analysis of Observational Epidemiological Studies

지도 남 정 모 교수

이 논문을 보건학석사 학위논문으로 제출함

2008년 6월

연세대학교 보건대학원

역학통계학과

황 예 원

황예원의 보건학 석사학위논문을 인준함.

심사위원 _____ 인

심사위원 _____ 인

심사위원 _____ 인

연세대학교 보건대학원

2008년 6월 일

감사의 말씀

늘 부족했던 저를 지도해주시고 따끔한 충고를 아끼지 않으신 남정모 교수님께 깊은 감사를 드립니다. 또한 미흡한 저의 논문을 심사해 주신 지선하 교수님과 대학원 과정동안 저에게 많은 가르침을 주신 보건대학원의 여러 교수님들께도 감사를 드립니다. 제자로 저를 길러주시고 성실함을 몸소 보여주시며 논문에 도움을 주신 김수영 교수님께도 깊은 감사드립니다.

2008년 6월

황 예 원

차 례

표 차 례

그 림 차 례

= Abstract =

Soy Food Consumption and the Risk of Prostate Cancer: A Meta-Analysis of Observational Epidemiological Studies

Yewon Hwang
Graduate School of Public Health
Yonsei University
(Supervised by Professor Chung Mo Nam, Ph.D.)

Context: Observational studies have suggested that higher consumption of soy foods may reduce the risk of prostate cancer.

Objective: We conducted a systematic review with a meta-analysis of studies that assessed the association between soy-based food consumption and the risk of prostate cancer.

Data sources and study selection: We searched MEDLINE, EMBASE, CINAHL, Korea Medical Database, KoreaMed, Koreanstudies Information Service System, Japana centra Revuo Medicina, and China National Knowledge Infrastructure for studies released through October, 2007. We manually searched the bibliographies from key retrieved articles, reviewed scientific evidence reports.

Data extraction and synthesis: Two authors independently extracted the data, including the study design, participant characteristics, measurement of soy food consumption and outcomes, adjustment for potential confounders, estimates of associations, and study quality criteria. We subgrouped the associations based on different types of soy consumptions. We pooled odds ratios (OR)

using a random-effects model.

Results: We identified five cohort studies and eight case-control studies.The pooled OR for all soy foods was 0.69 (95% CI, 0.57-0.84), and the OR for non-fermented soy foods was 0.75 (95% CI, 0.62-0.89). Among individual soy foods, only tofu yielded a significant OR (0.73; 95% CI, 0.57-0.92). The results were consistent and statistically significant in sensitivity analyses. Consumption of soy milk, miso, or natto did not significantly reduce the risk of prostate cancer. Genistein and daidzein were significantly associated with a lower risk of prostate cancer.

Conclusions: This systematic review suggest that soy food consumption may lower the risk of prostate cancer. Future research should attempt to make a defenite conclusion.

Keywords : soybean, prostate cancer, meta-analysis

I. INTRODUCTION

Prostate cancer is the second leading cause of cancer death among American men, after lung cancer. The American Cancer Society (ACS) estimates that in 2008, about 186,320 new cases of prostate cancer will be diagnosed in the United States, and about 28,660 men will die of the disease (ACS, 2007_1). While the underlying research outcomes are not yet clear, the ACS suggests that eating less red meat and fat and eating more vegetables, fruits, and whole grains may reduce the risk of prostate cancer (ACS, 2007_1; Fournier, 1998).

Soybean products are promoted as protective against certain type of cancer, and researchers believe that the isoflavones in soy (*e.g.*, genistein, daidzein, and glycitein) may play a role in reducing the risk of cancer. Isoflavones are sometimes called "plant estrogens" or "phytoestrogens," because they act like weak forms of estrogen, blocking cells from using other forms of estrogen (ACS, 2007_2). Indeed, a number of laboratory and animal experiments, as well as studies that observed large groups of people, have found that soy isoflavones may reduce the risk of developing breast, prostate, and colon cancer. Despite these findings, research has yielded mixed results as to whether consuming isoflavones can lower the risk of prostate cancer (Jacobsen, 1998; Nomura, 2004; Lee, 2003; Sonoda, 2004).

Only one meta-analysis actually correlated soy consumption with a lower risk of prostate cancer, and this analysis was funded by the soy food industry and has some methological limitations (Yan, 2005). First, it did not include studies assessing fermented soy food (such as miso and natto in Japan), because the authors thought that fermented food might increase the risk of certain cancers (Wu, 2000). However, to our knowledge, no studies have firmly demonstrated that consuming fermented soy foods correlated with prostate

cancer. Second, the analysis combined measurements from different types of soy foods, even though their effects might be of different magnitudes, and even though some may have had a positive effect and others a negative effect (Qin, 2006). Third, the study did not consider the race of the study populations, even though prostate cancer is most common in North America and northwestern Europe and less common in Asia, Africa, and Central and South America. The reasons for this discrepancy are not clear, but race should be considered as a potential stratification factor that might modify the effects of soy foods on prostate cancer risk.

Although it was not a systematic review, another review found inconsistencies between a few studies that demonstrated a statistically-significant protective effect, which should limit the contribution of these studies to the exposure-disease relationship (Ganry, 2005).

Since no pilot studies or human clinical trials have assessed the relationship between soy product intake and prostate cancer risk, we conducted a new systematic review and meta-analysis of the epidemiologic studies that describe the association between soy food consumption and the risk of prostate cancer. We gleaned our data from the original measurements of soy intake from each individual study, in order to accurately assess the effects of different types of soy foods. And we included an assessment of fermented soy food, with subgroup analysis to reveal any differences in the effects of fermented and nonfermented soy food (such as soy milk, tofu, soybeans, soynuts). Finally, to assess the contributions of race to prostate cancer risk, we conducted separate analyses for all men combined, men in Asia, and men in Western countries.

II. METHODS

1. Selection criteria

To be included, studies had to be cohort studies (prospective cohort or historical cohort) or case-control studies with an adult population. For the purpose of this report, all study arms with any type of soy product were considered "soy interventions." We included all methods for measuring exposure to soy, such as questionnaires, interviews, and serum level or urinary excretion of isoflavones. We did, however, excluded data concerning soy food consumption after cancer diagnosis, because dietary soy intake is easily changed. We limited our analyses to studies of clinical cancer outcomes (*e.g.*, diagnosis of prostate cancer). We did not include studies with tumor-related biomarkers or cancer risk factors as outcomes.

2. Search strategy

We conducted a systematic literature search of MEDLINE (1966 to October 2007), EMBASE (1980 to October 2007), and CINAHL (1982 to October 2007) for studies describing the association between soy food consumption and prostate cancer. Since many traditional foods in Korea, Japan, and China are prepared from soy, we reasoned that numerous studies could have been published in these three languages. Thus, we also searched the Korea Medical Database (KMbase) (http://kmbase.medric.or.kr), KoreaMed (http://www.koreamed.org, Korea Medical database), and KISS (Koreanstudies Information Service System, http://kiss.kstudy.com/) for studies in Korean;

Japana centra Revuo Medicina (JAMAS) (www.jamas.or.jp) for studies in Japanese; and China National Knowledge Infrastructure (CNKI) (www.cnki.co.kr) for studies in Chinese.

Two search themes, "soy" and "prostate cancer," were combined using the Boolean operator AND. The first theme, "soy," combined the synonyms of the Natural standard, and search terms of MEDLINE and EMBASE. The second theme, "prostate cancer," combined the search terms of MEDLINE and EMBASE.

These search terms were adapted to search MEDLINE and EMBASE:

#1. (soybeans[mh] or soybean oil[mh] or soy[tw] or soybean*[tw] or genistein[mh] or isoflavones[mh] or glycine max[tw] or coumestrol*[tw] or daidzein[tw] or edamame*[tw] or genistein[tw] or greater bean[tw] or isoflavon*[tw] or legume*[tw] or natto*[tw] or phytoestrogen*[tw] or plant estrogen[tw] or plant estrogens[tw] or soya[tw] or shoyu[tw] or soja[tw] or sojabohne[tw] or texturized vegetable protein[tw] or texturized vegetable proteins[tw] or Bowman-Birk trypsin inhibitor[tw] or inositol hexaphosphate[tw] or phytic acid[tw] or phytic acids[tw] or beta-sitosterol[tw] or saponin*[tw] or daidzein*[tw] or chinese pea extract[tw] or chinese pea extracts[tw] or bean extract[tw] or bean extracts[tw] or soyabean*[tw] or tofu[tw] or soyacal[tw])

#2. Prostatic Neoplasms[mh] OR prostatic neoplasm*[tw] OR prostate cancer*[tw] OR prostate neoplasm*[tw]

#3 #1 AND #2

To make our search as highly sensitive as possible, we didnot limit study designs, and we considered articles published in any language. In addition, we manually searched the reference lists of all identified relevant publications, reviewed selected scientific evidence reports (Agency for Healthcare Research

and Quality).

3. Review methods

A. Study Selection

Two reviewers (HYW and KSY) identified articles eligible for further review by performing an initial screen of identified abstracts or titles. Articles were retained when either of the two reviewers believed that it should be retained. The second screening was based on full-text review. Any disagreement was resolved by consensus.

B. Data extraction

Information on study design, participant characteristics, measurement of soy food consumption and outcomes, adjustment for potential confounders, and estimates of associations were extracted in parallel by two independent investigators. Discrepancies were resolved by discussion and repeated examination of the articles.

Both the measures used to quantify soy intake and the levels of soy intake varied considerably among the studies, so we examined the risk associated with the largest differences in exposure between their case groups and control groups. We extracted adjusted relative risks (RRs), hazard ratios, odds ratios (ORs), and 95% confidence intervals (CIs) for the risk of developing prostate cancer in a higher consumer compared to a lower consumer.

C. Quality assessment

We assessed how well the study was done to minimise the risk of bias or

confounding using checklist of Scottish intercollegiate guidelines network (SIGN). If few or no criteria have been fulfilled, the conclusions of the study were thought likely or very likely to alter. And we regarded the study as "study of low quality".

D. Statistical Analysis

The ORs were used as the common measure of association across studies by directly considering the hazard ratios and RRs as ORs. The meta-analysis was performed using Stata version 9.2 (StataCorp, College Station, Texas). We used the "meta" command in Stata, in order to generate a pooled OR across the studies, using the DerSimonian and Laird random-effects models (Egger, 2007, DerSimonian, 1986). Analyses were separated based on the type of soy food or isoflavone, whether the food was fermented, the race of study population, and the study design. Forest plots were used to visually assess the OR estimates and 95% confidence intervals (CIs) across the studies. Sensitivity analysis was performed to assess the effects of study quality.

To assess for heterogeneity of ORs across the studies, the Cochrane Q statistic (P = 0.10 was considered significant) and I^2 statistic were calculated (Higgins, 2003; Higgins, 2002). The possibility of publication bias was assessed using the Egger test and visual inspection of a funnel plot (Begg, 1994; Egger, 1997). To estimate whether publication bias would explain the observed associations, we also calculated "fail-safe N" using MetaWin 2.0 (Rosenthal, 1979).

Ⅲ. RESULTS

We identified five cohort studies and eight case-control studies (with no overlapping data) that investigated the link between soy food or isoflavone consumption and the risk for prostate cancer. The cohort studies included 87,844 participants and 1206 incident cases of prostate cancer (Table 1), and the case-control studies included 4018 cases and 4407 controls (Table 2). Four (Kurahashi, 2007; Allen, 2004; Nagata, 2007; Sonoda, 2004) of the studies were conducted in Japan, two (Jian, 2004; Lee, 2003) in China, one (Sung, 1999) in Taiwan, four (Nomura, 2004; Jacobsen, 1998; Severson, 1989; Strom, 1999) in the United States, one (Villeneuve, 1999) in Canada, and one (Kolonel, 2000) in the United States and Canada.

Table 1. Cohort studies of soy consumption and risk for prostate cancer

Source	Population	Total N/No. Of Cases	Soy Assessed	Soy Intake Comparison	Adjusted RR (95%CI)	Maximum Follow-up, year	Adjustment
Kurahashi, 2007	Japan/Japanese	43,509/307	genistein daidzein miso soup total soy	<13.2mg/d vs ≥32.8mg/d <8.5mg/d vs ≥20.4mg/d <110.0mL/d vs ≥356.0mL/d <46.6g/d vs ≥107.4g/d	0.71(0.48-1.03) 0.77(0.52-1.13) 1.04(0.72-1.50) 0.82(0.57-1.19)	9	age, area, smoking status, drinking frequency, marital status, BMI, intake of total fatty acids,dairy, vegetables and fruits
Allen, 2004	Japan/Japanese	18,115/196	tofu miso soup total soy	<2/week vs almost daily <2/week vs almost daily Low vs High	0.88(0.58-1.35) 0.94(0.67-1.33) 0.79(0.53-1.18)	33	age, calendar period, city of residence, radiation dose and education level
Nomura, 2004	Hawaii/Japanese American	5,826/304	tofu	0g/week vs >240g/week	0.82(0.54-1.23)	30	age, cigarette smoking, alcohol intake, total calories, arm muscle area, BMI
Jacobsen, 1998	California/not reported	12,395/225	soybean milk	never vs >1/day	0.3(0.1-0.9)	16	age, BMI, frequency of consumption of coffee, whole fat milk, eggs and citrus fruits, age at first marriage
Severson, 1989	Hawaii/Japanese	7,999/174	tofu miso soup	≤1/wk vs ≥5/day ≤1/wk vs ≥5/day	0.35(0.08-1.43) 1.24(0.51-3.04)	21	age

Abbreviations: RR, relative risk; BMI, body mass index.

Table 2. Case-control studies of soy consumption and risk for prostate cancer

Source	Population	No. Of cases/No. Of Controls	Soy Assessed	Soy Intake Comparison	Adjussted OR (95%CI)	Adjustment
Nagata, 2007	Japan/Japanese	200/200	isoflavones genistein daidzein	<30.5mg/d vs ≥89.9mg/d <1.1mg/d vs ≥2.5mg/d <0.8mg/d vs ≥1.9mg/d	0.48(0.25-0.93) 0.68(0.39-1.20) 0.64(0.36-1.17)	smoking, energy, PUFA intake
Sonoda, 2004	Japan/Japanese	140/140	Total soy tofu natto	≤77.0g/d vs ≥187.2g/d ≤19.7g/d vs ≥96.4g/d ≤5.7g/d vs ≥40.0g/d	0.53(0.24-1.14) 0.47(0.20-1.08) 0.25(0.05-1.24)	cigaretts smoking, energy intake
Jian, 2004	China/Chinese	130/274	fermented soy	0g/d vs>4.0g/d	2.02(1.08-3.78)	age, BMI, physical activity, locality of residence, education, family income, marital status,prostate cancer in first-degree relatives, caloric intake, fresh vegetables and fruits consumption, tea drinking
Lee, 2003]	China/Chinese	133/265	Total soy tofu genistein daidzein	<27.5g/d vs >111.8g/d <14.3g/d vs >34.5g/d <17.9mg/d vs >62.0mg/d <10.0mg/d vs >36.3mg/d	0.51(0.28-0.95) 0.58(0.35-0.96) 0.53(0.29-0.97) 0.56(0.31-1.04)	age, total calories
Kolonel, 2000	Canada, United States/multiethnic	1,619/1,618	Total soy African-American White Japanese Chinese	lowest vs highest quintile lowest vs 2nd tertile lowest vs highest tertile lowest vs highest tertile lowest vs highest tertile	0.62(0.44-0.89) 0.85(0.60-1.21) 0.77(0.45-1.30) 0.73(0.19-2.80) 0.74(0.37-1.44)	age, education, ethnicity, geographic area, calories
Strom, 1999	United states/Caucasian	83/107	genistein daidzein formononectin biochanin	high or low high or low high or low high or low	0.71(0.39-1.30) 0.57(0.31-1.05) 0.99(0.54-1.81) 0.92(0.50-1.70)	age, family history of prostate cancer, alcohol intake, total caloric intake
Villeneuve, 1999	Canada/multiethnic	1,623/1,623	soybean or tofu	none vs some	0.8(0.6-1.1)	age, province of residence, race, years since quitting smoking, cigarette pack-years, BMI, rice and pasta, coffee, grains, cereals, alcohol, fruit and fruit juices, meat intake, income, familoy history of cancer
Sung, 1999	Taiwan/South Mine, Hakka, Mainland	90/180	soybean milk	yes vs no	0.95(0.45-2.00)	-

Abbreviations: OR, odds ratio; BMI, body mass index; PUFA, polyunsaturated fatty acid.

Ten studies measured soy consumption using a self-questionnaire; the other three used an interview (Nagata, 2007; Kolonel, 2000; Jian, 2004). The evaluations addressed various soy interventions, such as total consumption of soy food and individual consumption of miso, tofu, soybean milk, natto, isoflavones, etc. Seven studies (Allen, 2004; Jacobsen, 1998; Severson, 1989; Kolonel, 2000; Strom, 1999; Villeneuve, 1999; Sung, 1999) did not report exposure differences using a quantitative scale (such as mg/day, g/week). Instead, these studies used frequency of consumption without reporting portion sizes, and tertiles or quartiles without reporting exact cut-off points, etc as comparisons.

The potential confounders for which the studies were adjusted are shown in Tables 1 and 2. All of the studies considered age as a potential confounder, but three (Allen, 2004; Severson, 1989; Sung, 1999) of the studies were not adjusted for the potential confounding factors of diet or caloric intake.

Among the thirteen selected studies, one cohort study (Jacobsen, 1998) and three case-control studies (Nagate, 2007; Lee, 2003; Kolonel, 2003) found an association between soy food consumption and decreased risk of prostate cancer. One case-control study (Jian, 2004) found that intake of fermented soy food increased the risk of prostate cancer.

1. Type of Soy Food or Isoflavone

In the analysis of individual types of soy food, only tofu demonstrated a significant protective effect with no heterogeneity (Table 3; Figure 1). Five studies (Allen, 2004; Nomura, 2004; Severson, 1989; Sonoda, 2004; Lee, 2003) tested the relationship between tofu and prostate cancer risk, and one case-control study (Lee. 2003) reported a significant relationship. The association between tofu consumption and prostate cancer was slightly stronger after we excluded two low-quality studies (Allen, 2004; Severson, 1989) (OR,

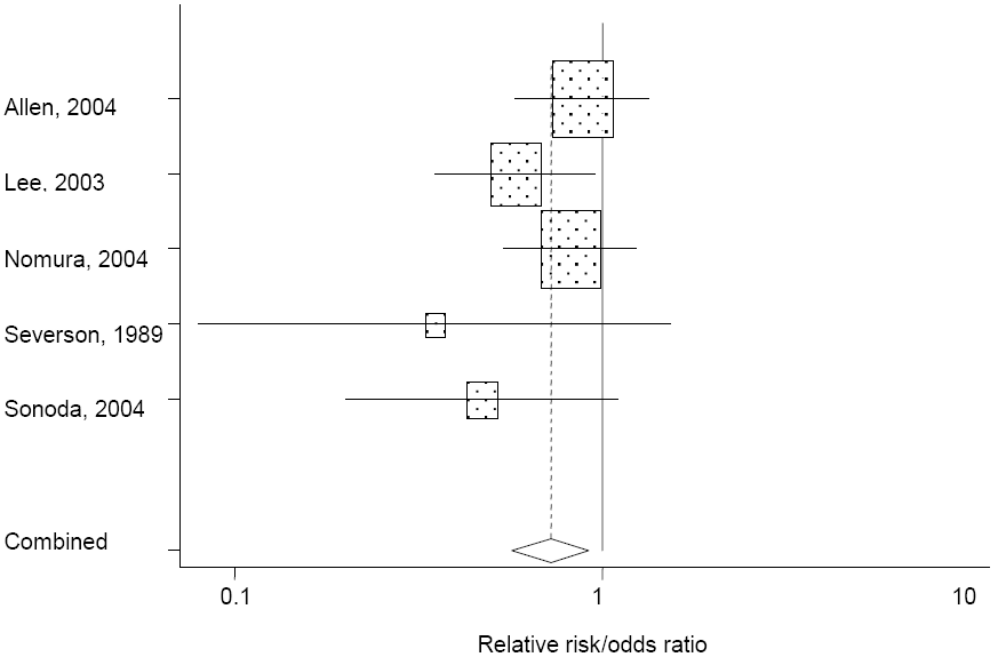
0.68; 95% CI 0.50-0.91; P =0.011; P for heterogeneity, 0.39).

Table 3. Summary odds ratios for the association between soy consumption and prostate cancer in cohort and case-control studies

	Studies	Pooled OR (95% CI)	P value	P value for heterogeneity	I^2 (%)
Type of soy food					
Tofu	5	0.73[0.57, 0.92]	0.009	0.428	0
Soybean milk	2	0.57[0.19, 1.76]	0.332	0.089	-
Natto	1	0.25[0.05, 1.25]	0.091	-	-
Miso	3	1.00[0.79, 1.27]	0.991	0.820	-
Total soy food	5	0.69[0.57, 0.84]	<0.001	0.544	0
Fermentation					
Yes	5	1.10[0.76, 1.57]	0.620	0.100	49
No	8	0.75[0.62, 0.89]	0.001	0.413	2
Type of soy isoflavone					
Genistein	4	0.67[0.52, 0.86]	0.002	0.873	0
Daidzein	4	0.66[0.51, 0.86]	0.002	0.772	0
Biochanin	1	0.92[0.50, 1.69]	0.789	-	-
Formonectin	1	0.99[0.54, 1.82]	0.974	-	-

Abbreviation: OR, odds risk; CI, confidence interval.

Figure 1. Relative risk/odds ratios for the associations between tofu consumption, for individual studies and all studies combined.



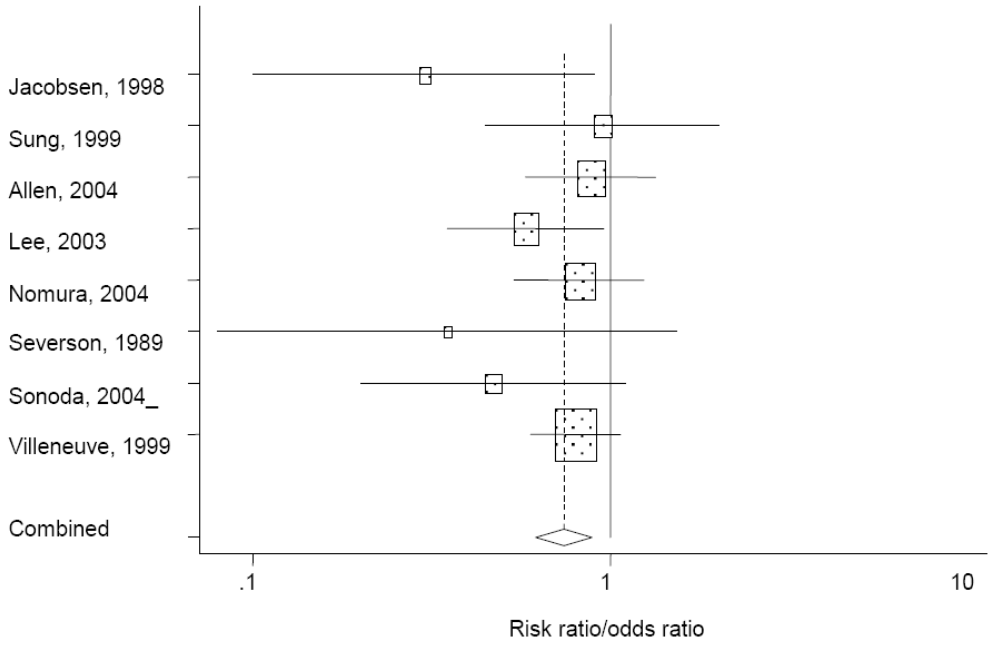
The size of the data markers (squares) corresponds to the weight of the study in the meta-analysis

The risk of prostate cancer decreased significantly in association with high consumption of non-fermented soy foods (including tofu, soybean milk, and soybeans), but high consumption of fermented soy foods (including miso and natto) was associated with an increased risk of prostate cancer. Excluding of two low-quality studies gave us similar results (OR, 1.08; 95% CI, 0.51-2.29; P=0.851).

Four cohort studies (Allen, 2004; Jacobsen, 1998; Severson, 1989), and four case-control studies (Sonoda, 2004; Lee, 2003; Villeuneuve, 1999; Sung, 1999) tested non-fermented soy food. Among these eight studies, one (Jacobsen, 1998) of the cohort studies and one (Lee, 2003) of the case-control studies

reported an inverse association between non-fermented soy food consumption and risk of prostate cancer. For the studies that reported an association between soy consumption and prostate cancer, the summary odds ratio (OR) was 0.75 (95% CI, 0.62-0.89; *P*= 0.001; *P* for heterogeneity=0.413; Figure 2).

Figure 2. Relative risk/odds ratios for the association between non-fermented soy food consumption, for individual studies and all studies combined.



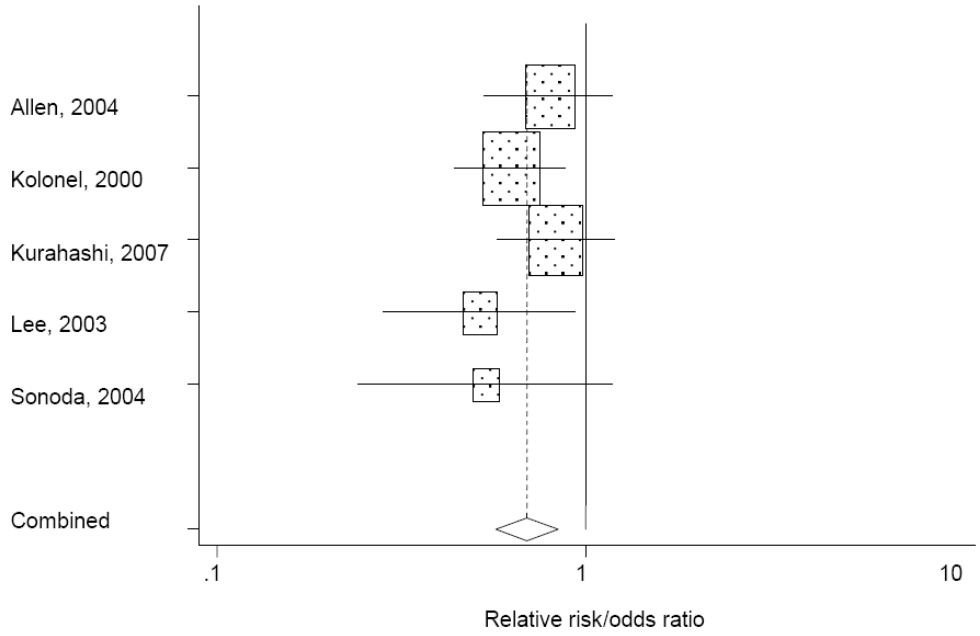
The size of the data markers (squares) corresponds to the weight of the study in the meta-analysis

A sensitivity analysis that excluded three low-quality studies (Allen, 2004; Severson, 1989; Sung, 1999) yielded a slightly stronger result, with a pooled OR of 0.69 (95% CI, 0.54-0.89; *P*=0.004; *P* for heterogeneity, 0.289).

One study (Kolonel, 2000) evaluated consumption of soy food without reporting original intake measurements for individual soy products (such as tofu, soybean milk, natto). Additionally, the results of four other studies were

based on combined measurements from fermented and nonfermented soy food. Although the overall combination of soy foods was diverse, we regarded this combination as possibly the most accurate description of the way most people consume soy food,-as a wide variety- so we combined these measurements as "total soy food". Among the five studies that evaluated total soy food consumption, two studies (Kolonel, 2000; Lee, 2003) concluded that it had a significant protective effect. The pooled OR was 0.69 (95% confidence interval [CI], 0.57-0.84; $P<0.001$), and the P value for heterogeneity in results was 0.54. Excluding one study of low quality (Allen, 2004), did not change the findings (OR, 0.66; 95%CI, 0.53-0.82; $P<0.001$). Figure 3 details the risk ratios for the associations between total soy food consumption, for individual studies and for all studies combined.

Figure 3. Relative risk/odds ratios for the associations between total soy food consumption for individual studies and for all studies combined.



The size of the data markers (squares) corresponds to the weight of the study in the meta-analysis

When we analyzed individual types of soy isoflavone, genistein (OR, 0.67; 95%CI, 0.52-0.86; P=0.002) and daidzein (OR, 0.66; 95%CI, 0.51-0.86; P=0.002) had significant protective effects, without heterogeneity.

2. Race of population

In the five studies that evaluated the association between total soy food consumption and prostate cancer, four studies enrolled Asian populations and one study (Kolonel, 2000) enrolled both Asian and Western subjects. Exclusion of the Western population did not change the findings, although there was no significant relationship between total soy food consumption and prostate cancer

in the Western population. We could not isolate Western population data for non-fermented soy food and tofu, because the majority of the studies were conducted in Asian and multi-ethnic populations.

3. Study design

The sensitivity analyses that included only cohort studies did not yield significant results, although they did reveal that the risk of prostate cancer tended to decrease with consumption of tofu, non-fermented soy food, and total soy food. In contrast, the analyses that included only case-control studies yield more significant protective effects for tofu, non-fermented soy food, and total soy food (Table 4).

Table 4. Subgroup analysis of soy consumption and prostate cancer according to study characteristics

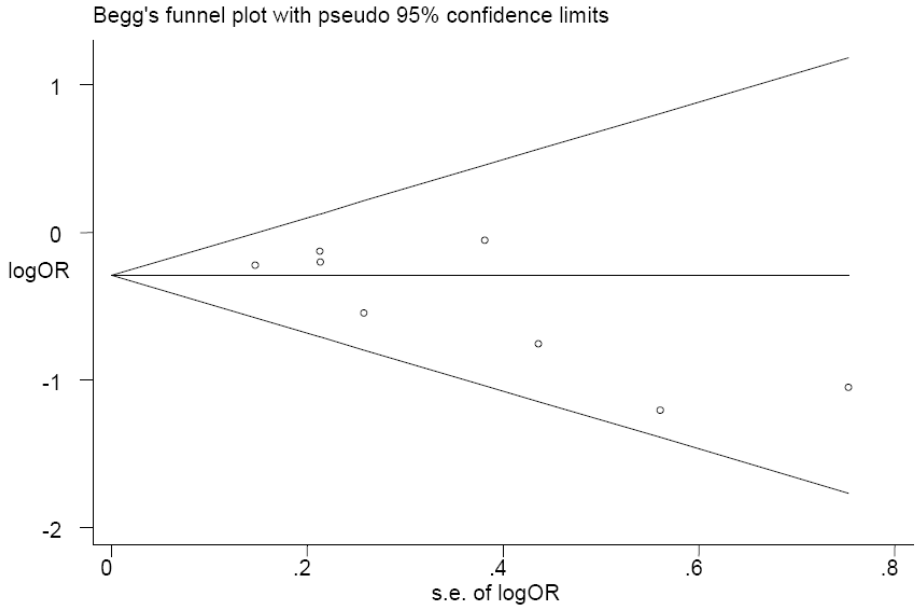
	Studies	Pooled OR (95% CI)	*P* value	*P* value for heterogeneity
Tofu	5	0.73[0.57, 0.92]	0.009	0.428
Cohort study	3	0.82[0.62, 1.10]	0.182	0.499
Case-control study	2	0.55[0.36, 0.85]	0.007	0.678
Non-fermented soy food	8	0.75[0.62, 0.89]	0.001	0.413
Cohort study	4	0.72[0.49, 1.06]	0.094	0.221
Case-control study	4	0.73[0.58, 0.92]	0.008	0.443
Total soy food	5	0.69[0.57, 0.84]	<0.001	0.544
Cohort study	2	0.81[0.62, 1.06]	0.116	0.892
Case-control study	3	0.58[0.44, 0.77]	<0.001	0.831

Abbreviation: OR, odds ratio CI, confidence interval

4. Assessment of Publication Bias

The Begg funnel plot was symmetic, and the Egger test provided no evidence of publication bias for the tofu (t=-2.62, *P*=0.079), and total soy food (t=-1.26; *P*=0.295). However, for the non-fermented soy food analysis, visual inspection of the Begg funnel plot (Figure 4) and the Egger test provided evidence for publication bias (t=-2.49, *P*= 0.047).

Figure 4. Funnel plot for non-fermented soy food



We calculated the number of studies with null results that would be required to eliminate significance we observed for these associations. These fail-safe numbers were 11.9 for tofu, 23.2 for total soy food, and 32.3 for the non-fermented soy food.

Ⅳ. DISCUSSION

The current meta-analysis supported a significant inverse association between soy food consumption and risk of prostate cancer. Subjects who consumed higher amounts of total and non-fermented soy food had a lower risk for prostate cancer, compared to those who consumed relatively less. An analysis regarding individual types of soy food suggested that this effect was due to consumption of tofu. Furthermore, the association persisted and remained statistically significant in sensitivity analysis performed to assess the potential effect of study quality. Natto, soybean milk, miso were only investigated in a few studies, so we can not conclude whether there consuming them has no effect, or that the effect of consuming these foods is masked by the small number of studies.

Additionally, in the pooled analysis, we observed similar inverse associations between genistein or daidzein intake and the risk of prostate cancer. Given this consistency, we concluded that a relationship could exist, but further studies are required to make a firm conclusion.

1. Validity of the studies and limitations of this review

However, the considerable variation in the amount of soy food ingested makes it impossible to draw anything but a qualitative conclusion. We can conclude that the associations may possibly exist, but the magnititude of the observed estimates are inexact.

Notably, we observed evidence of publication bias that might have led to asymmetry in the funnel plots. In these situations, the combined effect of the meta-analysis would overestimate the treatment's effect. Therefore, we investigated the statistical stability of the meta-analysis results- by calculating

the so-called fail safe numbers: the number of studies with negative data necessary to negate the significance of the observed associations. For the current analyses, these numbers were relatively small according to a commonly-used criterion that requires a fail-safe number to be (5n+10, where n is the original number of studies in the analysis) (Rosenthal, 1979)

The sensitivity analyses grouped according to study design demonstrated associations for case-control but not for cohort studies. The most likely underlying explanation for this situation is bias in recalling dietary intake (Malila, 1998): moreover publication of "positive" studies may have overestimated the association in the case-control comparisons. However, considering the tendency of reverse associations and the small number of selected studies, an authentic relationship may possibly exist, although we can not verify such a relationship in this review.

Another possible limitation is that people may consume different types of soy food that may or may not mediate different levels of protection-particulary fermented and non-fermented soy food. This fact makes it difficult to estimate the exact effect of individual soy foods. As shown in this study, the magnitude, and direction of the effects of individual soy food were quite different. To estimate the effect of one type of soy food, the primary study should have statistically adjusted data to that from consumption of another type of soy food.

This type of study is preliminary, because people who choose to eat soy may also make other lifestyle decisions that lower the risk of cancer (*e.g.*, lower fat intake, higher vegetable and fruit intake, more frequent exercise). Theoretically, these habits, rather than soy intake, could be behind the benefits seen in these studies. Among the selected thirteen studies, three did not consider any other lifestyle confounders, but we regarded these studies as being of poor quality, and we excluded them in the sensitivity analysis.

However, the quality of the studies did not seem to markedly influence the results.

Confounding variables are the most critical threat to the validity of results from cohort studies, whereas many more difficulties, selection bias in particular, arise in case-control studies (Egger, 2007). Among the eight case-control studies, only three studies enrolled community-based controls, and the others enrolled hospital-based controls. However, data were not sufficient to make a judgement as to how much selection bias influenced the outcome of the studies.

Lack of data concerning food composition (Peeters, 2003), as well as lack of information about the soy portion sizes that the subjects consumed (Jacobsen, 1998) complicated the dietary analysis. Only five studies addressed the validity of their questionnaires. Misclassification of soy intake may have occurred, due to measurement errors associated with the dietary instruments (Lee, 2003). However, such misclassification is often assumed to be nondifferential, leading to an underestimation of any true associations of dietary components and risk, rather than an overestimation (Wu, 1996).

Except for two of the cohort studies, the studies assessed soy food consumption only once; given the long follow-up period of many of the cohort studies, changes in soy food consumption among the subjects may weaken the observed associations (Davis 1991).

2. Mechanism

Soy and its isoflavone components have been studied scientifically in the context of numerous health conditions. Isoflavones such as genistein are believed to have estrogen-like effects in the body; as a result, they are sometimes called "phytoestrogens." In laboratory studies, however, it is not clear whether isoflavones stimulate or block the effects of estrogen; they may

do both, acting as mixed-receptor agonists/antagonists. Short-term intervention studies have shown that serum sex hormone-binding globulin concentrations are elevated in men who consume tofu (Habito, 2000; Habito 2001). In addition, intake of phytoestrogens may reduce cell proliferation and angiogenesis and increase apoptosis (Bylund, 2000; Zhou, 1999; Zhou, 2002).

3. Findings from other reviews

Yan *et al.* examined the relationship between soy intake and prostate cancer risk in a meta-analysis of epidemiologic studies. The meta-analysis included two cohort studies (Nomura, 2004; Jacobsen, 1998) and six case-control studies (Sonoda, 2004; Lee, 2003; Kolonel, 2000; Villeneuve, 1999; Strom, 1999; Sung, 1999). They concluded that consumption of soy foods correlated with an approximately 30% reduction in prostate cancer risk (Yan, 2005). Although our study revealed a similar finding, we made a more comprehensive methodological effort: we included a more complete literature search, conducted subgroup analyses by individual soy food or isoflavone, and peformed sensitivity analyses.

V. CONCLUSIONS

This systematic review suggest that higher soy food consumption may lower the risk of the prostate cancer. Although we selected a small number of primary studies, and the methodological differences between studies were large, the findings of our multiple analyses were consistent and corroborated previous study. It is possible that the weak estrogen-like effect of the isoflavones contained in soy might help prevent prostate cancer, but these results should be reflected in much more studies, for definite conclusions can be made. The results herein highlight the need for future research should attempt to establish whether this association is causal and to clarify the underlying mechanism.

REFERENCES

ACS. [Homepage on the Internet]. Bethesda: American cancer society; c-2007 [updated 2007 Jun 27;cited 2007 Oct 2]. Overview: Prostate cancer. What cause prostate cancer? Available from: http://www.cancer.org/docroot/CRI/CRI_2_1x.asp?dt=36

ACS. [Homepage on the Internet]. Bethesda: American cancer society; c-2007 [updated 2007 Jul 12;cited 2007 Oct 2]. Soybean. Available from:http://www.cancer.org/docroot/ETO/content/ETO_5_3X_Soybean.asp?siteare a=ETO

Allen NE, Sauvaget C, Roddam AW, et al. Prospective study of diet and prostate cancer in Japanese men. Cancer Causes Control 2004; 15: 911-20

Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50(4): 1088-101

Bylund A, Zhang JX, Bergh A, et al. Rye bran and soy protein delay growth and increase apoptosis of human LNCaP prostate adenocarcinoma in nude mice. Prostate 2000; 42: 304-14

Davis CE, Rifkind BM, Brenner H, et al. A single cholesteerol measurement underestimates the risk of coronary heart disease: an emperical example from the Lipid Research Clinics mortality follow-up study. JAMA 1990; 264: 3044-6

DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7(3): 177-188

Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315(7109): 629-34

Egger M, Smith GD, Altman DG. Systematic review in Health Care. Meta-analysis in context. BMJ books, 2007

Fournier DB, Erdman JW Jr, Gordon GB. Soy, its components, and cancer

prevention: a review of the in vitro, animal, and human data. Cancer Epidemiol Biomarkers Prev 1998; 7: 1055-65

Ganry O. Phyto-oestrogens and prostate cancer risk. Prev Med 2005; 41: 1-6

Habito RC, Ball MJ. Postprandial changes in sex hormones after meals of different composition. Metabolism 2001; 50: 505-11

Habito RC, Montalto J, Leslie E, et al. Effects of replacing meat with soyabean in the diet on sex hormone concentrations in healthy adult males. Br J Nutr 2000; 84: 557-63

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. BMJ 2003; 327(7414): 557-560

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21(11): 1539-1558

Jacobsen BK, Knutsen SF, Fraser GE. Does high soy milk intake reduce prostate cancer incidence? The Adventist Health Study. Cancer Causes Control 1998; 9: 553-7

Jian L, Zhang DH, Lee AH, et al. Do preserved foods increase prostate cancer risk? Brit J cancer 2004; 90(9): 1792-95

Kolonel LN, Hankin JH, Whittemore AS, et al. Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. Cancer Epidemiol Biomarkers Prev 2000; 9: 795-804

Kurahashi N, Iwasaki M, Sasazuki S, et al. Soy product and isoflavone consumption in relation to prostate cancer in Japanese men. Cancer Epidemiol Biomarkers Prev 2007; 16: 538-45

Lee MM, Gomez SL, Chang JS, et al. Soy and Isoflavone consumption in relation to prostate cancer risk in China. Cancer Epidemiol Biomarkers Prev 2003; 12: 665-8

Malina N, Virtanen M, Pietinen P, et al. A comparison of prospective and retrospective assessments of diet in a study of colorectal cancer. Nutr Cancer

1998; 32(3): 146-53

Nagata Y, Sonoda T, Mori M, et al. Dietary isoflavones may protect against prostate cancer in Japanese men. J Nutr 2007; 137: 1974-9

Nomura AM, Hankin JH, Lee J, et al. Cohort study of tofu intake and prostate cancer: no apparent association. Cancer Epidemiol Biomarkers Prev 2004; 13: 2277-9

Peeters PH, Keinan-Boker L, van der Schouw YT, et al. Phytoestrogens and breast cancer risk. Review of the epidemiological evidence. Breast Cancer Res Treat 2003; 77(2): 171-83

Qin LQ, Xu JY, Wang PY, et al, Soyfood Intake in the Prevention of Breast Cancer Risk in Women: A Meta-Analysis of Observational Epidemiological Studies. J Nutr Sci Vitaminol 2006; 52: 428-36

Rosenthal R. The "file-drawer" problem and tolerance for null results. Psychol Bull 1979; 86: 638-41

Severson RK, Nomura AM, Grove JS, et al. A Prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. Cancer Research 1989; 49: 1857-60

SIGN. [Homepage on the Internet]. Edinburgh: Scottish intercollegiate guidelines network; c-2001 [cited 2007 Oct 2]. Critical appraisal: Notes and checklists. Available from: http://www.sign.ac.uk/methodology/checklists.html

Sonoda T, Nagata Y, Mori M, et al. A case-control study of diet and prostate cancer in Japan: possible protective effect of traditional Japanese diet. Cancer Sci 2004; 95: 238-42

Strom SS, Yamamura Y, Duphorne CM, et al. Phytoestrogen intake and prostate cancer: a case-control study using a new database. Nutr Cancer 1999; 33: 20-25

Sung JFC, Lin RS, Pu Y, et al. Risk factors for prostate carcinoma in Taiwan. A case-control study in a Chinese population. Cancer 1999; 86: 484-91

Villeneuve PJ, Johnson KC, Kreiger N, et al. The Canadian cancer registries epidemiology research group. Risk factors for prostate cancer: results from the cancdian national enhanced cancer surveilance system. Cancer Causes Control 1999; 10: 355-67

Wu AH, Yang D, Pike MC. A meta-analysis of soyfoods and risk of stomach cancer: the problem of potential confounders. Cancer Epidemiol Biomarkers Prev 2000; 9: 1051-8

Wu AH, Ziegler RG, Horn-Ross PL, et al. Tofu and risk of breast cancer in Asian-Americans. Cancer Epidemiol Biomarkers Prev 1996; 5(11): 901-6

Yan L, Spitznagel EL. Meta-analysis of soy food and risk of prostate cancer in men. Int. J. Cancer 2005; 117: 667-9

Zhou JR, Gugger ET, Tanaka T, et al. Soybean phytochemicals inhibit the growth of transplantable human prostate carcinoma and tumor angiogenesis in mice. J Nutr 1999; 129: 1628-35

Zhou JR, Yu L, Zhong Y, et al. Inhibition of orthotopic growth and metastasis of androgen-sensitive human prostate tumors in mice by bioactive soybean components. Prostate 2002; 53: 143-153

국문요약

콩 섭취와 전립선암의 위험: 관찰연구의 메타 분석

배경 : 관찰 연구들에서 콩 음식 섭취가 전립선암의 발생을 감소시킬 수도 있다고 제시되었으나 명확한 결론은 내려지지 않았다.

목적 : 콩 음식이나 보충제 섭취와 전립선 암의 발생과의 관계를 평가한 관찰연구들을 메타 분석하고 체계적으로 고찰하고자 한다.

자료원과 연구 선택 : 2007년 10월까지의 자료를 PubMed, Embase, CiNAHL, Korea Medical Database, KoreaMed ,Koreanstudies Information Service system, JAMAS, China Academic journal를 이용해 검색하였다. 전자 검색된 자료의 참고문헌을 수기 검색하고 근거 보고서를 리뷰하였다.

자료 추출과 자료 통합 : 두 명의 리뷰 저자가 독립적으로 표준화된 자료 추출 양식을 사용해 연구 설계, 주요 질문, 대상자의 수와 특성, 콩 섭취량의 측정, 추적 관찰기간, 결과변수와 효과의 크기, 보정한 혼란변수의 보정 자료를 추출하였다. 무작위 효과 모형을 이용해 pooled OR을 구하였다.

결과 : 총 코호트 연구 5편과 환자-대조군 연구 8편이 선택되었다. 전체 콩 음식에 대한 pooled OR은 0.69(95% CI, 0.57-0.84)였고 콩 비 발효 음식에 대한 pooled OR은 0.75(95% CI, 0.62-0.89)였다. 개별 콩 음식 중 두부만 pooled OR 0.73(95%CI, 0.57-0.92)였고 두유, 미소, 낫도는 결과가 유의하지 않았다. 콩 성분 중 genistein과 daidzein이 유의한 결과가 나왔다

결론 : 콩 음식 중 발효 음식, 특히 두부는 전립선암의 발생을 감소시킨다. 향후 이런 연관성과 기전을 명확히 하는 임상시험이 필요하다.

핵심단어 : 콩, 전립선암, 메타분석