RESEARCH ARTICLE

Phytoestrogen Intake and Risk of Ovarian Cancer: a Meta-Analysis of 10 Observational Studies

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Abstract

Background: Epidemiology studies have shown an inconclusive relationship between phytoestrogen intake and ovarian cancer risk and there have been no relevant meta-analyses directly regarding this topic. The purpose of the present meta-analysis was therefore to investigate any association between phytoestrogen intake and ovarian cancer in detail. Materials and Methods: We conducted a search of PubMed, EMBASE, EBSCO, the Cochrane Library, CNKI and Chinese Biomedical Database (up to April 2014) using common keywords for studies that focused on phytoestrogen and ovarian cancer risk. Study-specific risk estimates (RRs) were pooled using fixed effect or random-effect models. Results: Ten epidemiologic studies were finally included in the meta-analysis. The total results indicated higher phytoestrogen intake was associated with a reduced ovarian cancer risk (RR, 0.70; 95%CI: 0.56-0.87). The association was similar in sensitivity analysis. Meta regression analysis demonstrated sources and possibly types and regions as heterogeneous factors. Subgroup analysis of types, sources and regions showed that isoflavones (RR: 0.63; 95%CI: 0.46, 0.86), soy foods (RR: 0.51; 95%CI: 0.39, 0.68) and an Asian diet (RR: 0.48; 95%CI: 0.37, 0.63) intake could reduce the incidence of ovarian cancer. Conclusions: Our findings show possible protection by phytoestrogens against ovarian cancer. We emphasize specific phytoestrogens from soy foods, but not all could reduce the risk. The habit of plentiful phytoestrogen intake by Asians is worthy to recommendation. However, we still need additional larger well designed observational studies to fully characterize underlying associations.

Keywords: Phytoestrogen - ovarian cancer - meta-analysis - isoflavones - soy food

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Introduction

Ovarian cancer is the sixth most common cancer in women (Andres et al., 2011; Srisuttayasathien et al., 2013) and the third female reproductive malignant tumors in worldwide. The mortality of ovarian cancer is in the fifth place among cancer-related death in Western societies (Zhao et al., 2011). Those do put a serious threat to women's health.

Phytoestrogen is a group of plant-derived compounds that naturally mimic or antagonize endogenous estrogens, to promote or inhibit estrogenic responses (Tamaya 2005; Kim et al., 2012). Phytoestrogen can bind to estrogen receptors (ERs) because it's structural similar with estradiol (E2, 17β-estradiol). Phytoestrogen has much weaker ER-binding affinity than that of estradiol, and it plays diverse role on the regulation of reproductive system (Ososki et al., 2003). The major categories of phytoestrogen are flavones (Kaempferol, Quercetin), isoflavones (genistein, dadizine, Glycitein, Formononetin), ligans (enterolactone, enterodiol and nordihydroguaiaretic acid) and coumestans (coumestrol) (Jefferson et al., 2012; Woclawek-Potocka et al., 2013). They are rich in soy-derived foods, which have drawn enough attentions for several decades in Asian people's diet. What's more, red clover, flax seed, grape-containing products, vegetables have been recently studied (Woclawek-Potocka et al., 2013). For its estrogen-like property, evidences from *in vitro* studies, back in 1997, have suggested an inverse association between phytoestrogen intake and ovarian cancer risk in cell lines like SK-OV-3cells (Choi et al., 2007; Gossner et al., 2007), OVCAR-3 cells (Luo et al., 2008) and cell lines from patients (Gercel-Taylor et al., 2004; Green et al., 2009; Ning et al., 2012). Epidemiology studies have done in recent decades. However, the results are controversy. What's more, to date there have been no relevant meta-analyses directly regarding this topic.

The purpose of this meta-analysis was to investigate the association between phytoestrogen intake and ovarian cancer risk. Also, using the summary statistics, we could assess the possible association between the type, source of phytoestrogen intake and the risk of ovarian cancer.

Materials and Methods

Data sources and searches

We searched MEDLINE (PubMed), EMBASE, EBSCO, the Cochrane Library, CNKI and Chinese

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Biomedical Database by common keywords as follows: phytoestrogen(s), isoflavone(s) (genistein, daidizein, glycitein, formonectin), ligans, coumestants (coumestrol), soy (soya, soybean, tofu), ovarian cancer (tumor, neoplasm) and epidemiology (cohort, case-control). We also browsed the references of included articles to find any additional studies.

Selection criteria

Articles were included if they met all of the following criteria: 1) a case-control or cohort study, 2) evaluated the association between phytoestrogen intake and ovarian cancer risk, and 3) reported the adjusted odds ratios (OR) or relative risks (RR) and 95%confidence intervals (CI).If publications were duplicated or shared in more than one study, the first publication was included. Excluded from this analysis were studies that evaluated phytoestrogen as a dietary supplement.

Data extraction and quality assessment

Two authors independently search the databases and extract data according to the selection criteria. The form of extracted data were as follows: study name (first author's name and year of publication), journal name, Region and design, study period (in years), duration for follow-up, participation (mean age), measure of phytoestrogen intake, adjusted OR or RR with 95%CI and adjustments.

The quality of the studies was judged by the Newcastle-Ottawa Scale (Wells et al.,) on three perspectives: the selection of study groups, comparability of groups, and ascertainment of either the exposure or outcome of interest, respectively. One more star for an energy adjusted residual or nutrient density models was added according to Wan-Shui Yang's meta-analysis (Yang et al., 2011). Thus, the full score was 10 stars, and the high-quality study was defined as a study with no less than 7 stars.

Statistical analysis

Phytoestrogen intake (highest versus lowest intake) and the risk of ovarian cancer were identified in this meta-analysis. We used the most-adjusted OR or RR to calculate the summary RR. When studies reported RR or OR separately for different source or different type of phytoestrogen, inverse-variance method was used to recalculate the pooled RR by combined these subgroups into a single one independently (Manzoli et al., 2007; Dong et al., 2011). Heterogeneity was tested using Cochrane's test and I2 statistics (Higgins et al., 2003). Homogeneity was accepted if the P value was >0.1 and I^2<50% and random effect model was chosen by using the method of DerSimonian and Laird (1986). Otherwise, we used fixed effect model and calculated by inverse variance method (Woolf, 1955). Subgroup analyses were performed by study design (cohort or case-control studies), type of phytoestrogen intake (isoflavones, ligans, coumestants, flavones), source of phytoestrogen intake and region (Asians or non-Asians).

Publication bias was assessed with Egger et al. (1997) or Begg's tests (Begg et al., 1994). If a significant publication bias or high heterogeneity existed, we conducted a meta regression analysis and sensitivity analysis to assess the stability of combined RR and the possible influence or sources of the bias. Statistical analysis was performed with Stata SE version 12.0 (Stata Corporation, College Station, TX).

Results

Data searches and the characteristics of the data

3719 articles were obtained from the database. We initially identified 12 studies that met the selection criteria after we screened the titles and abstracts of all the studies (McCann et al., 2003; Zhang et al., 2004; Sakauchi et al., 2007; Chang et al., 2007; Gates et al., 2007; 2009; Rossi et al., 2008; 2010; Wang et al., 2009; Hedelin et al., 2011; Bandera et al., 2011). Then, we reviewed the full texts of the remaining articles. Among these, two studies shared the same region and we excluded the recent one for no RR and 95%CI reported (Rossi et al., 2010). One study performed the RR of phytoestrogen on total cancer risk, not ovarian cancer, solely (Wang et al., 2009).We picked up a newest study by checking on pubmed again (Lee et al., 2014). Finally, we included 10 studies in our analysis.

The 10 studies, with 4 cohort studies and 6 case-control studies, totally included 4392 cases and 293500 controls. The characteristics of the studies in this analysis were summarized in Table 1. The studies conducted in following countries: USA (n=5), China (n=2), Japan (n=1), Swedish (n=1), Italy (n=1). Nine studies separated the OR according to the different types of phytoestrogen and four did not report the total estimated size. One studies just showed Tofu as total phytoestrogen intake. Two studies reported isoflavones and two studies reported flavones as the total phytoestrogen intake. Potential confounders were considered and adjusted in all studies.

Quality assessment is summarized in Table 2 and 3. The range of the studies was 6 to 9. The rate of high-quality studies was 80%.

Overall and subgroup analysis

As shown in Figure 1, high phytoestrogen intake was significantly associated with reduced risk of ovarian cancer (summary RR: 0.70; 95%CI: 0.56, 0.87). Statistically heterogeneity was existed in this analysis (Q=31.76, p=0.001, I^2=71.76%). No publication bias observed from Begg's test (p=0.372), but showed in Egger's test (p=0.04). Among high-quality studies, the summary RR was 0.70 (95% CI: 0.53, 0.91).

As a significantly heterogeneity existed, sensitivity analysis was conducted. The results are shown in Figure 1. The summary RR changed from 0.66 (95%CI: 0.52, 0.82) to 0.74 (95%CI: 0.60, 0.92) via exclusion of the study by Gates and Lee. A regression analysis was performed. The results are shown in Table 4. The analysis showed sources of phytoestrogens was one of the heterogeneous factors (p=0.041). Region (p=0.072 or 0.125) and type (p=0.082) were possible heterogeneous factors.

Then we performed subgroup analysis. When stratified by study design, a higher inverse effect was observed in case-control studies (RR: 0.65; 95%CI: 0.48, 0.89), not in cohort studies (RR: 0.77; 95%CI: 0.53, 1.10). We further conducted subgroup analysis on source, type and

Table 1. Characteristics of the Studies Included in the Final Analysis (n=10)

First author	Year	Country	Control source	Follow-up	Participants	Measure of soy intake	Adj. OR or RR (95% CI)
Case-control studies							
McCann[a]	2003	USA	Population	--	124 cases, 696 controls	Total lignan (ug/d): >708 vs <304 Quercetin (ug/d): >31708 vs <10165 Kaempferol (ug/d): >8569 vs <2089	0.43(0.21-0.85) 0.71(0.38-1.32) 0.73(0.39-1.34)
Zhang[b]	2004	China	Population	--	254 cases, 652 controls	Total isoflavones(mg): ≥32.8 vs ≤11.6 Daidzein (mg): ≥14.9 vs ≤5 Genistein (mg): ≥20.9 vs ≤6.6 Glycitein (mg): ≥1.7 vs ≤0.4 Soy foods (g/day): ≥136.4 vs ≤ 47.0 Tofu (beancurd) (g): ≥45.1 vs ≤10	0.51(0.31-0.85), 0.52(0.31-0.87), 0.50(0.30-0.84), 0.59(0.35-0.97), 0.50(0.31-0.82), 0.35(0.22-0.58)
Rossi[c]	2008	Italy	Hospital	--	1301 cases, 16050 controls	flavones (mg/day): >173.6 vs <67.3, Isoflavone (ug/day): >32.5 vs <12.8	0.79(0.60-1.04), 0.51(0.37-0.69)
Bandera[d]	2011	New Jersey	Population	--	205 cases, 390 controls	Phytoestrogens (mcg/10^3 kcal):≥1287.82vs<532.28 Isoflavones(mcg/1000 kcal): ≥404.67 vs < 70.06, Daidzein (mcg/1000 kcal): ≥144.08 vs < 20.25, Genistein (mcg/1000 kcal): ≥247.86 vs < 40.46, Glycitein (mcg/1000 kcal): ≥9.18 vs < 2.14, Total lignans(mcg/1000 kcal): ≥704.76 vs < 271.22 Total soy foods: ≥one cup/month vs never	0.77(0.45-1.19), 0.86(0.52-1.42), 0.88(0.53-1.46), 0.83(0.50-1.38), 0.80(0.48-1.33), 1.1(0.68-1.79), 0.71(0.42-1.2)
Gates[e]	2009	USA	Population	--	1141cases, 1183 controls	Total flavonoid(mg/day) : >27.5 vs <6.0 Quercetin(mg/d): >16.5 vs <3.5 Kaempferol(mg/d): >6.9 vs <0.5	1.06(0.78-1.45), 1.14(0.84-1.56), 0.98(0.73-1.32)
Lee[f]	2014	China	Population	--	500cases, 500controls	Total soy foods (g) > 119.0 vs ≤61.4 Isoflavones (mg) > 41 vs ≤26.7 Daidzein (mg) >16.9 vs.<10.2 Genistein (mg) >21.1 vs 12.3 Glycitein (mg) >3.3 vs. ≤1.9	0.29(0.20-0.42), 0.45(0.29-0.59), 0.41(0.29-0.59), 0.42(0.30-0.60), 0.38(0.27-0.55)
Cohort studies							
Chang[g]	2007	USA	Prospective	8	280 cases among 97275 women	Total Isoflavone (mg/day): >3 vs <1, Genistein(mg): >1.1 vs ≤0.3, Daidzein (mg): >0.9 vs ≤0.3, Tofu (mg): ≥10 vs 0, meat substitutes: any vs None	0.56(0.33-0.96), 0.65(0.42-1.02), 0.75(0.49-1.16), 0.76(0.46-1.24), 0.83(0.55-1.27)
Sakuchi[h]	2007	Japan	Prospective	15	77 ovarian cancer death cases among 63541 women	Soybean curd(tofu) (times/week): Almost every day versus 1-2	0.61(0.26-1.45)
Gates[i]	2007	USA	Prospective	18	347 cases among 66940 women	Total flavonoid intake (mg/d) >42.6 vs <8.5 Quercetin(mg/d) >30.7 vs <6.3 Kaempferol(mg/d) >11 vs <0.8	0.57(0.25-1.29) 0.80(0.55-1.16) 0.60(0.42-0.87)
Hedelin[j]	2011	Swedish	Prospective population	16	163 cases among 47140 women	Total isoflavonoids(mg/d.MJ) 0.5 vs 38(Mean), Total lignans(mg/d.MJ) 528 vs 225(Mean), Coumestrol(mg/d.MJ) ≥ 0.014 vs None	0.43(0.21-0.85) 0.71(0.38-1.32) 0.73(0.39-1.34)

[a]Adjusted for age, education, menstruating, difficulty becoming pregnant, contraceptive use, menopausal status, energy intake; [b]Adjusted for age ,BMI education, area, smoke, alcohol, tea , physical activity, menarche, parity, menopausal status, hormone replacement therapy, contraceptive use, ovarian cancer in first-degree relatives; [c]Adjusted for age, study center, education, year of interview, parity, contraceptive use , family history of ovarian in first-degree; [d]Adjusted for age, education, race, major reproductive risk factors, BMI, total calories, smoking and physical activity; [e]Adjusted for age, oral contraceptive use, parity, history of tubal ligation, smoking status, history of postmenopausal hormone; [f]Adjusted for age ,BMI, physical activity, energy intake, parity, oral contraceptive use, hormone replacement therapy , menopausal status , education, smoking status, alcohol drinking , family history of ovarian or breast cancer; [g]Adjusted for Race, energy intake, parity, oral contraceptive use, strenuous exercise, wine and menopausal status, hormone therapy use; [h]Adjusted for age, menopausal status, number of pregnancies, history of sex hormone use, BMI, physical activity, education; [i]Adjusted for age, contraceptives, age at menarche, parity, hormone replacement therapy, energy intake, alcohol, saturated fat, meat, fish; [j]Adjusted for age, duration of oral contraceptive use, parity, history of tubal ligation, smoking status, history of postmenopausal hormone use, physical activity, lactose intake, and total energy intake

Table 2. Quality Assessment of Case-Control Studies Included in the Meta-Analysis

	Selection[a]				Comparability[b]		Exposure[c]			Model[d]	Scores
McCann, 2003	☆	☆	☆	☆	☆☆	☆	☆	-	-		8
Zhang, 2004	☆	☆	☆	☆	☆☆	☆	☆	-	-		8
Rossi, 2008	-	☆	-	☆	☆☆	☆	☆	-	-		6
Gates, 2009	-	☆	☆	☆	☆☆	☆	☆	-	☆		8
Bandera, 2011	-	-	-	☆	☆☆	☆	☆	-	☆		6
Lee, 2014	☆	☆	-	☆	☆☆	☆	☆	-	-		7

[a]Four stars could be awarded for item Selection for four aspects: adequate case definition; case representativeness; selection of controls; controls definition; [b]The item Comparability could get a maximum of 2 stars for enough controlled confounder; [c]Three stars could be awarded for item Exposuse for three aspects: exposure assessment; ascertainment of exposure; Non-exposure rate (no significant difference in the response rate between control subjects and cases by using the chi-square test); [d]Data analysis that used an energy-adjusted residual or nutrient-density model

Table 3. Quality Assessment of Cohort Studies Included in the Meta-Analysis

	Selection[a]				Comparability[b]		Exposure[c]			Model[d]	Scores
Chang, 2007	-	☆	☆	☆	☆☆	☆	☆	☆	☆		9
Sakuchi, 2007	☆	☆	☆	☆	☆☆	☆	☆	☆	-		9
Gates, 2007	-	☆	☆	☆	☆☆	☆	☆	☆	☆		9
Hedelin, 2011	-	☆	☆	☆	☆☆	☆	☆	☆	-		8

[a]Four stars could be awarded for item Selection for four aspects: adequate case definition; case representativeness ; selection of controls; controls definition; [b]The item Comparability could get a maximum of 2 stars for enough controlled confounder; [c]Three stars could be awarded for item Exposuse for three aspects: exposure assessment; ascertainment of exposure; Non-exposure rate (no significant difference in the rate between control subjects and cases by using the chi-square test); [d]Data analysis that used an energy-adjusted residual or nutrient-density model

Table 4. Meta Regression Analysis of Ten Studies

Analysized factors	exp	Std. Err.	P value	95% CI	tau2[a]
Year	1.01	0.037	0.8	0.93- 1.10	0.09
Study designb	1.22	0.28	0.43	0.71- 2.09	0.08
Sourcec	1.19	0.08	0.04	1.01-1.39	0.07
Typed	0.18	0.09	0.08	-0.08-0.38	0.05
Regione	1.51	0.36	0.12	0.87-2.63	0.06
Region by statef	1.16	0.08	0.07	0.98-1.37	0.04

[a]tau2, REML estimate of between-study variance; [b]Study design for case-control study and cohort study; [c]Source as phytoestrogens intake from soy foods and non-soy foods; [d]Type as isoflavones, flavones, ligans, coumestrol; [e]Region as Asian and non-Asian; [f]Region by state as USA, China, Japan, Swedish, Italy

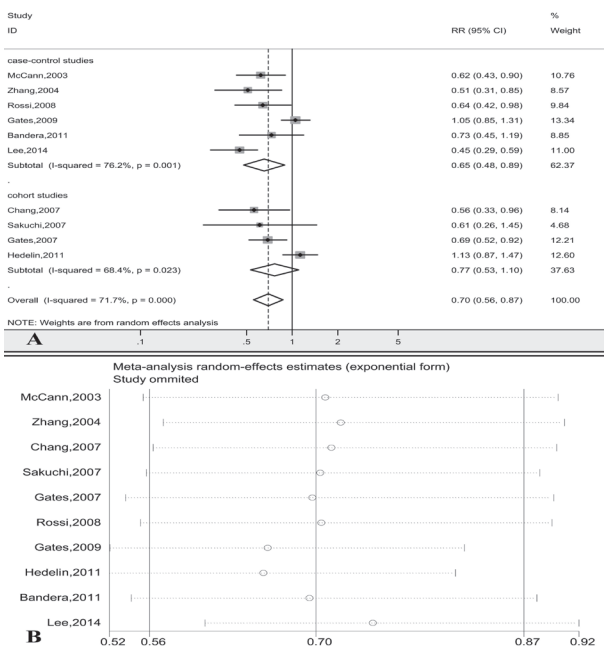

Figure 1. Phytoestrogen Intake and the Ovarian Cancer Risk by Random Effect Model (A) and Sensitivity Analysis (B). (**A**) RR, relative risk; CI, confidence interval. A combined protective effect showed in this figure. Black squares indicate the risk ratio. The square sizes represent the weight of each study. The combined risk ratio and its 95% CI is denoted by the hollow diamond; (**B**) Y axis represents the study omitted. The middle vertical line represents total summary RR (exponential form); the vertical lines on both sides represent the upper and lower limits of 95%CI; circles represent recalculated summary RR and horizontal lines represent recalculated 95%CI

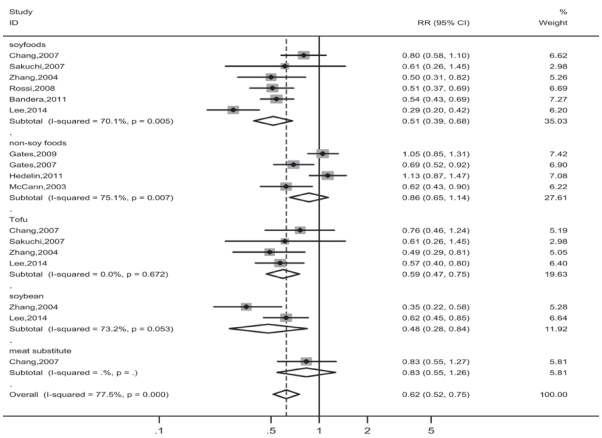

Figure 2. Subgroup Study Stratified by Food Source of Phytoestrogens. RR, relative risk; CI, confidence interval. A combined protective effect showed in this figure. Black squares indicate the risk ratio. The square sizes represent the weight of each study. The combined risk ratio and its 95% CI is denoted by the hollow diamond

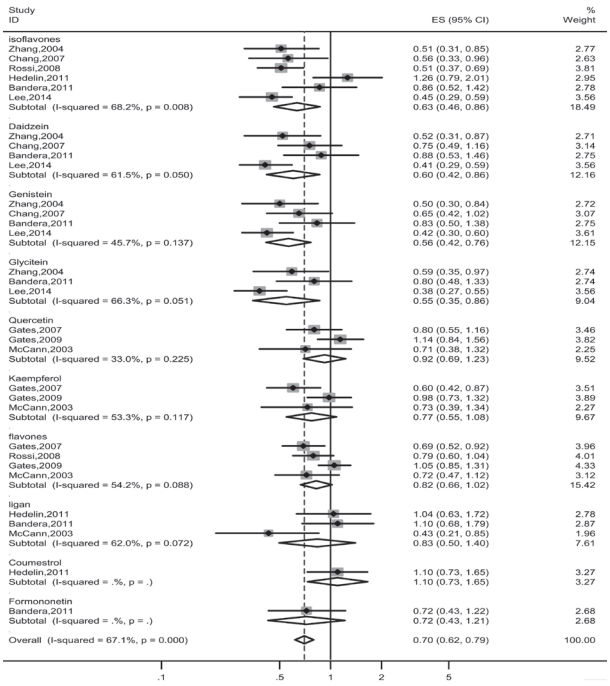

Figure 3. Subgroup Study Stratified by Type of Phytoestrogens (n=10). RR, relative risk; CI, confidence interval. A combined protective effect showed in this figure. Black squares indicate the risk ratio. The square sizes represent the weight of each study. The combined risk ratio and its 95% CI is denoted by the hollow diamond

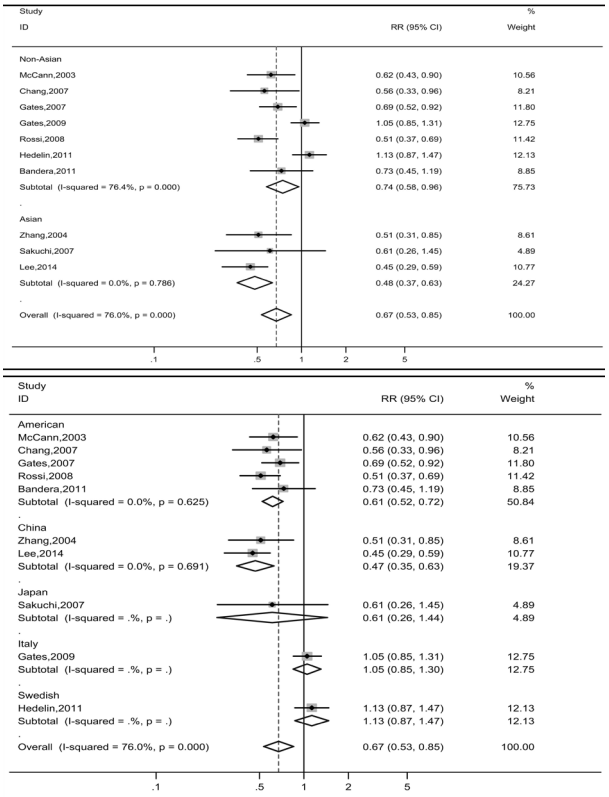

Figure 4. Subgroup Study Stratified by Region (n=10). (**A**) Region was simply classified into Asian and non-Asian; (**B**) Region was classified by per state as American, China, Japan, Italy, Swedish. RR, relative risk; CI, confidence interval. A combined protective effect showed in this figure. Black squares indicate the risk ratio. The square sizes represent the weight of each study. The combined risk ratio and its 95% CI is denoted by the hollow diamond

region. As shown in Figure 3 and 4, significant protective effects were seen in soy foods (RR: 0.51; 95%CI: 0.39, 0.68). Significant protective effect was also observed in isoflavones (RR: 0.63; 95%CI: 0.46, 0.86) and its subtypes like Dadizein (RR: 0.60; 95% CI: 0.42, 0.86), Genistein (RR: 0.56; 95%CI: 0.42, 0.76), Glycitein (RR: 0.55; 95%CI: 0.35, 0.86). When stratified by region, the protective effect of phytoestrogens on ovarian cancer risk was found significantly among women in Asian countries (RR=0.48, 95% CI: 0.37, 0.63).

Discussion

In our current analysis, higher phytoestrogen intake had a potential protective effect against ovarian cancer when compared to lower phytoestrogen intake (~30% reduced). The association was similar in sensitivity analysis by omitting study one by one. The protective effect was much stronger when omitted the most weighted study by Gates et al. (2007) and no publication bias observed from egger's test (p=0.170). A reduced heterogeneity was seen via exclusion study by Lee et al. (2014). Generally, we considered the result relatively stable and reliable.

There are several plausible mechanisms regarding phytoestrogen intake and ovarian cancer risk. One is the well-known ER-dependent signal transduction. Genistein, for example, share a similar structure with estradiol and can bind to ER, particularly ER-β, which is a very important role in regulating ER-stimulated estrogenic signal mechanisms (Lee et al., 2014). The other signal pathways are mediated by receptors like GnRH-receptor, FSH or LH receptors and GFR to regulate hormones' concentrations and the related genes' and proteins' expressions like Akt, Raf, caspase3, NF-ϰB, Bcl-2 (Leung et al., 2007; Banerjee et al., 2008), thus, inhibit apoptosis, metastasis and cell proliferation of ovarian cancer cells.

From the meta regression analysis, we considered the source of phytoestrogen was one of the heterogeneous factor. Subgroup studies found stronger protection of phytoestrogen intake from soy foods against ovarian cancer. Results from analysis of study region showed a significant protective effect of phytoestrogen in Asians, not in non-Asians. The protect effect was much stronger in China when we further classified the region per state. This difference may be caused by much more soy food intake in Asians or because soy food was the life-long diets in Asians, a long term effect was much more obvious. To this point, Asian diet of soy food intake was worth to recommend.

In separated analyses of studies that showed data on type of phytoestrogen intake, we found isoflavones was associated with ~37% reduction in ovarian cancer risk and non-isoflavones phytoestrogen (flavones, ligans, coumestrol) were observed negative effects. This suggested that isoflavones may play the most important role in protective effects of phytoestrogen. To our knowledge, isoflavones have positive effects on the survival of several cancers like breast cancer (Kang et al., 2012; Zhang et al., 2012), prostate cancer (Sugiyama et al., 2013); however we still know very little about the relationship between isoflavones intake and ovarian cancer risk. This study is the first one to undertake a detailed analysis of the relationship between isoflavones, flavones, ligans, the total phytoestrogen intake and ovarian cancer risk. Genistein, a widely studied isoflavone, was observed a slightly higher reduction in ovarian cancer risk, which was similar to *in vitro* studies and some *in vivo* animal studies. *In vitro* studies, Genistein was found to inhibit cell proliferation of SK-OV-3 (Choi et al., 2007), Caov-3 (Chen et al., 2001; Gossner et al., 2007) and OVCAR-3 (Chen and Anderson, 2001) cells and had cytotoxic effect on CHO (Rucinska et al., 2007) and BG-1 ovarian cancer cells. Also, genistein could inhibit the growth of ovarian cancer cells by regulation of the genes related to cell apoptosis like caspase-3, Bcl-2 (Solomon et al., 2008) and cell growth like VEGF (Luo et al., 2008). Furthermore, an *in vivo* study confirmed that genistein had a significant antitumor activity in dimethylbenz[a] anthracene (DMBA)-induced ovarian cancer in female Sprague Dawley rats (Luo et al., 2008).

Because the 8 of 10 studies we included were of high qualities, it was important to note that there was one study suggesting no association between isoflavones intake on ovarian cancer risk. And, more importantly, some other animal studies put forward the adverse effects. Genistein could lead to multioocyte follicles (Jefferson et al., 2002) and a higher frequency of ovarian granulosa cell tumor (Dorward et al., 2007). Meantime, Genistein stimulated the growth of ovarian cancer cells in a dose-dependent manner (Dorward et al., 2007). Although a statistical protective association was saw in this mata-analysis, more good-designed cohort or randomized controlled trials are still needed to ensure this conclusion.

Like all meta-analysis, some potential limitations existed in our analysis. First, among the ten studies we included, six studies were case-control studies. For their retrospective nature, case-control studies had more obvious recall bias and selection bias. For example , the use of food frequency questionnaires in case-control studies, in which recall bias was a problem, led to more measurement error and may affect the results. These biases could bring about spurious results and it was hard for us to avoid. Second, the number of the adjusted confounding factors differed among these studies. Energy intake which had been suggested to associate with cancer risk, for example, had been adjusted in only four of the nine studies. Therefore, the protective effect of phytoestrogen intake on ovarian cancer may be caused by other protective factors related to phytoestrogen. Third, the studies we analyzed used different measurement methods of phytoestrogen intake and different criterions of high and low exposure levels. The actual intake dose had very great difference, especially between Asians and Non-Asians. We compared the studies of Chang et al. (2007) and Zhang et al. (2004; 2012), the high level of isoflavones intake in USA was much lower than the low level of isoflavones intake in China. Therefore, we failed to assess the dose-response relationship between phytoestrogen intake and risk of ovarian cancer, which may be the focus of the future research. The last, heterogeneity existed across our studies. It may come from studied phytoestrogen source, type, region, and adjusted confounding factors in these studies.

In summary, our analysis of current epidemiology studies showed possible protection of phytoestrogens against ovarian cancer. We emphasized specific phytoestrogen from soy foods, but not all could reduce the risk of ovarian cancer. The habit of helpful phytoestrogen intake in Asians was worth to recommend. Our study need to be confirmed in future by larger well designed observational studies. Stronger assessment tools for phytoestrogen intake are warranted to fully characterize such an association and work out the possible cut-off point.

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