REVIEW ARTICLE

Dietary isoflavones and gastric cancer: A brief review of current studies

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Background: Although several *in vitro* and animal studies have suggested that isoflavones might exert inhibitory effects on gastric carcinogenesis, epidemiologic studies have reported inconclusive results in this field. The aim of this brief review was to investigate whether such an association exists among dietary isoflavones and gastric cancer incidence, prevention, and mortality in epidemiologic studies. **Materials and Methods:** We conducted a search of PubMed, Google Scholar, Cochrane, Science direct, and Iranian Scientific Databases including Scientific Information Database and IranMedex Database (up to November 2014) using common keywords for studies that focused on dietary isoflavones and gastric cancer risk. **Results:** A total of nine epidemiologic studies consisting of five case-controls, three prospective cohorts, and one ecologic study were included in this review. An inverse association between dietary isoflavones and gastric cancer was shown in only one case-control and one ecologic study. **Conclusion:** In summary, whether anticarcinogenic properties of isoflavones are established, research found no substantial correlation in this field. There are insufficient studies to draw any firm conclusions about the relationship between isoflavones intake and the risk of gastric cancer. Hence, further evidence from cohort and trial studies are needed.

Key words: Dietary isoflavones, flavonoids, gastric cancer

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INTRODUCTION

Stomach cancer is the second leading cause of cancer-related deaths worldwide.[1] Thus, gastric cancer prevention is one of the most important elements in all cancer control plans around the world.[2]

Various food types and nutrients are closely linked to gastric cancer.[3] It has been demonstrated that high consumption of salty foods and N-nitroso compounds cause to increase gastric cancer risk. In contrary, some dietary modifications such as high intake of fruits, vegetables, and soy products might decrease this risk.[4] Furthermore, it seems that a diet rich in isoflavones, as an indicator of dietary intake of foodstuffs of plant origin including chick pea, alfalfa, and peanut[5] and particularly soy beans,[6] may be able to prevent gastric cancer.[2] Various isoflavones include genistein, daidzein, biochanin A, and formononetin.[7] The most abundant isoflavone is genistein,[8] while daidzein is metabolized in the gut to equol which is a more biologically active metabolite than other isoflavones.[9] Due to the ability of dietary isoflavones to modulate several metabolic pathways,[10] their anti-cancer properties in some malignancies were shown. Initially, the effects of soy isoflavones on hormone-dependent cancers such as breast cancer and prostate cancer were related to their estrogen-like activities.[11] Other suggested mechanisms for their anticancer activities might be related to antioxidant and anti-inflammatory properties.[12]

Although the reports did not have the same results about isoflavone and gastric cancer, a negative association in this field might be due to high concentration of salt and N-nitroso compounds in some soy products, as the main sources of isoflavones. These conflicting

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evidences have been shown only in studies conducted among Asian countries[14] such as Japan and Korea, which have substantially varied intakes of isoflavones.[2]

Since the soflavones are structurally similar to 17β-estradiol, have a particular affinity for the β-estrogen receptor and may be able to have favorite effects on gastric cancer.[12] On the other hand, according to a report, gastric cancer has a greater economic impact and, estimating the economic burden of it, including health care expenditures and morbidity for patients and their families, is increasingly an important issue for health care systems.[13]

Thus, considering conflicting evidence around possible effects of dietary isoflavones on tumors[14-18] including gastric cancer, this brief review was conducted to better understand the effects of dietary isoflavones on prevention, incidence and mortality of gastric cancer in human populations including adult men and women.

MATERIALS AND METHODS

Search strategy

Following the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis, a literature search using PubMed, Google Scholar, Cochrane, Science direct, and Iranian scientific databases including Scientific Information Database and IranMedex was conducted for studies published up to November 2014 using the search terms ("isoflavones" [tiabs] or "soy isoflavones" [tiabs] or "phytoestrogens" [tiabs] or "soy" [tiabs]) and ("gastric cancer" [tiabs] or "gastric neoplasms" [tiabs] or "stomach cancer" [tiabs] or "stomach neoplasms" [tiabs]) to identify all available studies of the association among dietary isoflavones intake and gastric cancer prevention, incidence, and mortality. No restriction was applied. The reference lists of retrieved relevant articles were screened for additional primary studies.

Eligibility criteria

The eligibility of relevant papers was checked. We included studies if they were conducted on human populations and provided data on the association among different types of isoflavones found in dietary sources and gastric cancer incidence, prevention, and treatment. Exclusion criteria include:

1. *In vitro* and animal experimental studies,
2. No reported data on isoflavones intake or gastric cancer, and
3. No reported data on the relationship between these variables.

Furthermore, review papers were excluded from this study.

Study selection

Having removed duplicates, the relevant papers were selected. First, the titles and abstracts of identified papers were screened and irrelevant papers were excluded. Then, the full texts of these articles were explored by two independent reviewers. A flow chart showing the selection process of our review is presented in Figure 1.

Data extraction and abstraction

Based on the study design, significant change for each study including odds ratio or relative risk values was extracted. In addition, the extracted information from the eligible papers was as follows: First authors name, publication year, study design, study location, age and sex of participants, sample size, assessment method, *P*-value and statistical adjustments, and reported outcome.

Quality assessment

To assess the quality of included articles, a system based on Newcastle-Ottawa scale[19] was used. The full score was 10 and the high or median quality study was defined as a study with ≥7 or 4-7, respectively. In summary, three studies had high quality, three studies were medium quality, and there were two studies with low quality scores.

Methodological approaches to appraise the cohort and case-control studies are illustrated in Tables 1 and 2.

RESULTS

Through full text examination of potential publications, we identified 9 eligible articles including 3 cohorts, 5 case controls and one ecological study. Summary of these studies were shown in Table 3.

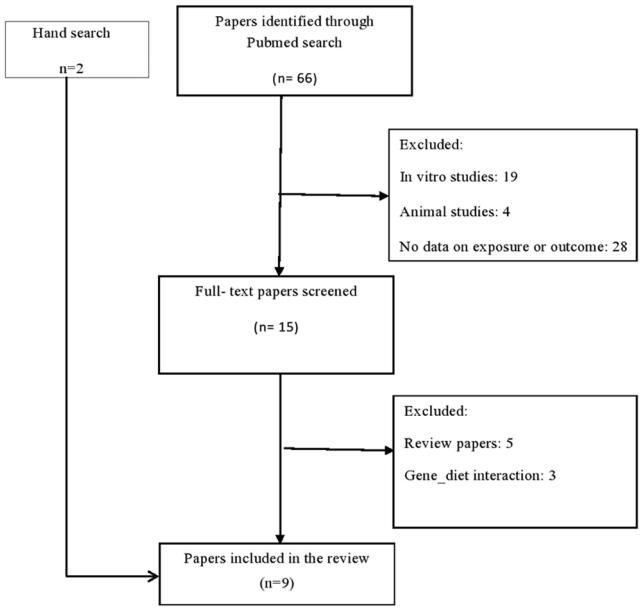

Figure 1: Flow chart of systematic literature search

Table 1: Methodologic quality of case-control studies included in the systematic review

First author, year of publication (reference)	Adequate definition of cases	Representativeness of cases	Selection of control subjects	Definition of control subjects	Control for important factor or additional factor	Exposure assessment	Same method of ascertainment for all subjects	Nonresponse rate	Data analysis that used an energy- adjusted residual or nutrient-density model	Total quality scores
Nomura *et al.* 2003[21]	*		*	*	*		*			5
Lagiou *et al.* 2004[20]	*				*		*		*	4
Ko *et al.* 2010*[4]*			*	*	**	*	*			6
Hara *et al.* 2013(3)		*	*	*	**	*	*			7
Woo *et al.* 2014[22]	*			*	**		*		*	6

Table 2: Methodologic quality of cohort studies included in the systematic review

First author, year of publication (reference)	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Data analysis that used an energy- adjusted residua l or nutrient-density model	Total quality scores
Nagata *et al.* 2002[11]	*		*	*	*	*		*	*	7
Hara *et al.* 2012[2]	*		*		*	*		*	*	6
Kweon *et al.* 2013[12]	*		*	*	*	*		*	*	7

Table 3: Summary of observational studies on the association between isoflavone intake and risk of gastric cancer

References	Study	Subjects	Exposure assessment	Adjustment for	Main findings	*P* value or *P* trend
Study design: cohort study Exposure assessment: dietary intake						
Nagata *et al.* 2002[11]	Tatayama study, Japan, prospective cohort design, 7 years of follow up	13880 men and 16424 women at least 35 years of age, 121 deaths from cancer	Semi quantitative FFQ (169 items)	Total energy, age, smoking, BMI, marital status, age at menarch, salt intake and rice, intake of coffee, History of participation in stomach cancer Screening for 3 years prior to entry into the study	No markedly association Men 0.63 (0.33-1.21) Women 0.54 (0.23-1.27)	- -
Hara *et al.* 2012[2]	JPHC study, Japan, prospective cohort design, 806 550 person years of follow up	39569 men and 45312 women aged 45-74, 1249 new gastric cancer cases	FFQ (138 items)	Age, public center area, BMI, smoking, drinking, family history of gastric cancer, intake of vegetable, fruit, fish, salt and total energy	Significant association only in women using exogenous female hormone Men 1.00 (0.81-1.24) Women 1.07 (0.77-1.50)	 0.96 0.6
Kweon *et al.* 2013[12]	SWHS (1996-2000) and SMHS (2000-2006) China, prospective cohort design	74941 women aged 40-70 61482 men aged 40-74, total of 493 Cases (211 men and 282 women	SWHS FFQ (77 items) SMHS FFO (81 items)	Age, BMI, metabolic equivalents hours per week per year, chronic gastritis history, family gastric cancer history, born in urban shanghai, family income, ever drink, ever smoke and smoking amounts at baseline examinations; and average intakes of total calorie, red meat, vegetables, sodium and fruits excluding watermelon; and menopausal status	No association HR (95%CI) All 0.86 (065-1.13) Men 0.85 (0.57-1.27) Women 0.87 (0.60-1.26)	 0.31 0.38 0.55
Study design: nested case control study Exposure assessment: blood isoflavone levels						
Ko et al. 2010[4]	KMCC study, Korea, nested case control design within multicenter community based prospective cohort	131 GC cases matched with 393 controls, 1 case matched with 3 controls, including89 male mean age 63.7 And 267 female mean age 62.8	Blood levels	age, sex, residence area, year of recruitment, smoking, H. pylori infection	Significant association genistein 0.54 (0.31-0.93) daidzein 0.21 (0.08-0.58) equol 0.50 (0.27-0.90)	 0.0346 0.0009 0.0228
Hara *et al.* 2013[3]	JPHC study, japan, 1990-2004, nested case control study within a large population based prospective study	483 GC cases matched to 483 controls, mean age 57.6±7.2	Blood concentrations	Sex, age, study area, date of blood collection and fasting time at blood collection, smoking, drinking intake of salted fish, salt, BMI, family history of GC, H.pylori infection	No significant association OR (95%CI) Total Genistein 0.96 (0.64-1.44) Daidzein 1.11 (0.74-1.66) Men Genistein 0.88 (0.54-1.44) Daidzein 1.04 (0.64-1.70) Woman Genistein 1.09 (0.48-2.47) Daidzein 1.00 (0.46-2.15)	 0.9 0.6 0.7 0.97 0.8 0.9
Study design: case control study						

(Continued)

Table 3: (Continued)

References	Study	Subjects	Exposure assessment	Adjustment for	Main findings	*P* value or *P* trend
Exposure assessment: dietary intake						
Nomura *et al.* 2003[21]	Survey, united states	300 cases (186 men and 114 women) and 446 population based controls (282 men and 164 women) aged 26-90	Quantitative FFQ (over 250 items)	Sex, age ethnicity	No association	-
Lagiou *et al.* 2004[20]	survey, Greece, 1981-1984, case-control design	110 incident cases of GC aged 64.5 and 100 control patients With orthopedic disorders aged 59.8	FFG (80 items)	Age, sex, place of birth, BMI, height, education, smoking, drinking, total energy intake, and vegetable intake	No inverse association OR (95%CI) Isoflavones 1.16 (0.73-1.84)	0.538
Woo *et al.* 2014[22]	Survey. Korea, case-control study	334 cases and 334 matched controls (208 male and 126 female in each group) aged 35-75	FFQ (103 items)	Energy intake, H.pylori, age, sex, education , smoking, drinking, BMI, activity, intake of pickled vegetables, and red and processed meat and fruits and vegetables	No association Total 0.85 (0.54-1.35) Men 0.98 (0.56-1.73) Women 0.67 (0.31-1.47)	0.400 0.694 0.259
Study design: ecological study Exposure assessment: dietary intake						
Nagata *et al.* 2000[23]	Survey, Japan	About 6000 randomly selected households in 12 districts covering 47 prefectures	Annual 3-day records	Mean age, smoking, drinking, salt intake	Marginally Pearson correlation coefficiencies Male r=0.27 Women r=0.13	0.06 0.08

Among these researches, six and two studies used food frequency questionnaires (FFQ) and plasma concentrations of isoflavones, respectively, to measure the dietary intake of isoflavones. In addition, in one study, 3 days dietary records were administered to estimate these intakes. Potential confounding factors were adjusted in these researches.

Case-control studies

A nested case-control study[3] was conducted involving gastric cancer cases and healthy controls. Cases had a lower body mass index and more *Helicobacter pylori* infection than controls, but other variables did not differ between two groups. Participant's isoflavones intake was assessed using blood concentrations of isoflavones. Results indicated that total plasma isoflavones concentrations and plasma concentrations of either daidzein or genistein were not significantly associated with gastric cancer risk. This null association is possibly due to the residual effect of established causes of gastric cancer, such as cigarette smoking, even after adjustment.

Findings in another same study,[4] demonstrated that higher blood concentrations of each isoflavones including genistein, daidzein, and equol could decrease gastric cancer risk. The combination of highest concentrations for each isoflavones suggests a stronger inverse association.

Another study provides evidence about no inverse association between dietary isoflavones intake and the risk of stomach adenocarcinoma.[20] In this study, cancer patients were older and less educated compared to the controls.

Another same study emphasized no relationship between total dietary isoflavones intake evaluated by using a FFQ and distal gastric adenocarcinoma.[21]

Furthermore, in a Korean population,[22] it was revealed that total isoflavones consumption could not display an important role on changing the gastric cancer risk in either men or women. However, it should be mentioned that the main dietary sources of isoflavones in this research had a high salt content which was not adjusted in any models and therefore could affect the results.

Cohort studies

Moreover, in this field, men and women were included in a prospective cohort study in Japan.[2] A single validated FFQ was used to calculate dietary isoflavones intake. During 806,550 person-years of follow-up, 1249 new cancer cases were identified including 899 men and 350 women. Results from this investigation found adherence to high isoflavones diet had no substantial effects on gastric cancer prevention among men and women. However, an increasing trend of this associated risk with higher isoflavones intakes was observed among women who used exogenous female hormones. This might be as a result of estrogen antagonist activity of isoflavones in a high estrogen environment.

The same results were suggested in a Chinese population.[12] A total of 493 distal gastric cancer cases were discovered during 1996-2010. Mean of two validated FFQs was computed to obtain exposure level, which reduced the misclassification of intakes.

During a community-based cohort study,[11] the link between isoflavones intake and death related to stomach cancer was examined. Through 7 years of follow-up among participants, 121 deaths occurred. After comparison of the highest and lowest quartiles of total dietary isoflavones and cancer death, there was no markedly association even after full adjustment for established confounding factors.

Other study designs

In this regard, an ecological analysis in 12 geographical districts covering 47 prefectures in Japan[23] showed dietary isoflavones intakes promotes a marginally inverse correlation with stomach cancer mortality in men. In crude analysis, similar results were obtained for women. However, after adjustment for mean age, total energy intake, smoking, drinking, and salt intake, the results for women changed toward the null with no change in results for men.

DISCUSSION

To our knowledge, this is the first review of literature to assess the effects of dietary isoflavones intake on gastric cancer incidence, prevention, and mortality. Four out of five case-control studies showed no protective effects of isoflavones against gastric cancer risk. In three of these studies, the dietary data were collected by FFQs which are subjected to information bias. Hence, the true relation between the exposure and outcome can be diluted.[4] Another study reported a significant reverse association between plasma isoflavones concentrations and gastric cancer risk. This finding may be due to the blood isoflavones assessment which reflects individual variability and it attenuates measurement error in the dietary assessment of FFQ-based relative risks. Blood concentration of isoflavones also provides not only an intake index, but also absorption and metabolism of isoflavones in each subject are being considered. However, the sample size in mentioned study was small which might increase the false positive results.[4]

Although the protective roles of isoflavones on gastric cancer incidence and mortality are not confirmed in cohort studies,[2,10,11] in one cohort study, there was an inverse association among exogenous female hormone users.[2] This finding can be explained by estrogen antagonist activity of isoflavones exhibited in estrogen rich environments. In cohort studies included in this paper, dietary intake of isoflavones was also surveyed by means of FFQs, which can be a limitation.

In one ecological study, a marginal inverse correlation between isoflavones intake and stomach cancer mortality was observed.[19] This impact did not change after adjustment for confounding factors in men but it shifted toward the null in women. Using diet records and large sample size were considered as the strengths of this study. However, due to sample selection based on household units and unavailability of some data such as age and sex, there could be some bias in the results.

While some experimental studies demonstrate that isoflavones can be used as an anticancer agent against stomach cancer cells,[24] humans studies mostly do not support the previous results. However, since human studies have been limited to observational epidemiologic designs, caution is needed in the results interpretation. Case-control studies with short time and cohort studies with follow-up <10 years may not be able to show the true effect because it has been shown that the isoflavones were more likely to be beneficial if their consumption had been initiated before puberty or during adolescence.[24,25]

The potential mechanisms of anticarcinogenic effects of isoflavones on gastric cells remain unclear [26,27]. A biologically plausible pathway is through antioxidative effects of these components that protect cells against oxidative damage by reducing lipid peroxidation products.[28] Furthermore, anti-inflammatory properties of isoflavones have been indicated by inhibiting transcription factors in nitric oxide (NO) production pathway. Thus, proinflammatory activities of NO are suppressed.[29] Another potential mechanism is competitively binding of isoflavones to the estrogen receptors in human gastric mucosa. This effect may be due to the similar structure of isoflavones to estradiol. Therefore, they suppress the carcinogenic effects of

estrogen.[30] Genistein also plays a role as a tyrosine kinas inhibitor.[31,32] Tyrosine kinase activities are associated with critical growth factor receptors which have been identified in some cells in stomach tumors. Hence, genistein is able to inhibit the autophosphorylation of these receptors; therefore, the proliferation or angiogenesis in these tumor cells is inhibited.[33]

In addition, it has inhibitory effects on the expression of cyclin D1, a regulator of cell cycle progression and the key protein on cell proliferation. This impact in cancer cells would help recovering of normal cell cycle and controlling proliferation speed of tumor cells.[34]

Besides, genistein can inhibit tumor cell proliferation by increasing the expression of cyclin B1, which is a regulatory protein involved in mitosis.[34,35] This isoflavone can down-regulate and up-regulate the Bcl-2, an anti-apoptotic protein, and Bax, a pro-apoptotic protein expression, respectively, which triggers the apoptosis of primary gastric cancer cells.[36] Moreover, genistein via suppression of cyclooxygenase-2 enzyme, which plays a crucial role in carcinogenesis, has antiproliferative and proapoptotic effects on gastric cancer cells.[37]

Furthermore, daidzein is known to serve as an apoptotic agent by up-regulating of PARP, caspase 9, caspase 3, and Bax proteins, which are all apoptotic factors. In addition, it decreases the expression of Bcl-2 protein.[38]

Like all reviews, some potential limitations existed in our study. First, among the nine studies we included, five studies were case-control studies. They have more obvious recall and selection bias because of their retrospective nature. As previously mentioned, using FFQ in some case-control studies causes recall bias and more measurement errors that may affect the results. Second, the number of adjusted confounding factors such as smoking and drinking differed among these studies. Energy intake which had been suggested to associate with cancer risk had been adjusted in only five studies. Therefore, the protective effects of isoflavones intake on gastric cancer may be caused by other protective factors related to phytoestrogen.

CONCLUSION

In summary, whether anticarcinogenic properties of isoflavones are established, research found no substantial correlation in this field. There are insufficient studies to draw any firm conclusions about the relationship between isoflavones intake and the risk of gastric cancer. Further evidence from observational and trial studies is warranted to identify the actual effects of these components on gastric cancer incidence, prevention, and mortality.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTIONS

All authors have contributed in designing and conducting the study. All authors have assisted in preparation of the first draft of the manuscript or revising it critically for important intellectual content. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

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