REVIEW

Epidemiological Evidences on Dietary Flavonoids and Breast Cancer Risk: A Narrative Review

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Abstract

Epidemiological studies on associations between intake of flavonoids and breast cancer risk are highly needed to assess the actual effects of flavonoids in humans. Experimental investigations *in vitro* conditions cannot detect and model the real action of these phytochemicals due to the limitations to consider absorption and metabolic biotransformation as well as several complex interactions. Therefore, the data about association findings between intake of flavonoids and breast cancer risk are compiled and analyzed in the current review by evaluating both the results obtained using food composition databases as well as different biomarkers. Although several case-control studies demonstrate some reduction in breast cancer risk related to high consumption of flavones and flavonols, large-scale prospective cohort studies with follow-up times of many years do not confirm these findings. Intake of isoflavones can be associated with a decrease in breast tumorigenesis only in Asian countries where the consumption of soy foods is high but not among Western women with significantly lower ingestion amounts, suggesting the presence of so-called threshold level of effect. Besides doses, the timing of exposure to isoflavones seems also to be a significant factor as childhood and prepubertal age can be critical periods. Although women may need to consume high amounts of isoflavones typical to Asian diets to gain beneficial effects and protection against mammary carcinogenesis, it is still too early to give any specific recommendations to prevent breast tumors by diet rich in certain flavonoids.

Keywords: Flavonoids- breast cancer risk- dietary intake- biomarkers- epidemiological studies- menopausal status

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Introduction

Prevention is a crucial component for reduction of the global burden of cancer morbidity and mortality (Hui et al., 2013). It has been recently suggested that about one-third to half of the most commonly diagnosed cancers in the Western world, including breast cancer, could be avoided by practicing healthy lifestyles, such as eating a healthy diet rich in plant-based products (Ingram et al., 1997; Bouker and Hilakivi-Clarke, 2000; Hui et al., 2013). Indeed, diets containing plenty of fruits and vegetables have been related to a decreased risk of carcinogenesis, whereas polyphenolic flavonoids are thought to exert important chemopreventive effects (Iwasaki et al., 2009b; Hui et al., 2013; Magne Nde et al., 2015). However, although the cell culture investigations and animal experiments have suggested the anticancer action of different flavonoids, the results from epidemiological studies have identified limited, inconsistent and even controversial evidences about the associations between dietary flavonoid consumption and the risk of breast cancer in humans (Yamamoto et al., 2003; Adebamowo et al., 2005; Fink et al., 2007; Travis et al., 2008; Zhu et al., 2011; Hui et al., 2013; Touvier et al., 2013; Zamora-Ros et al., 2013; Wang et al., 2014; Magne Nde et al., 2015). One of the most compelling hints about the protective effects of flavonoids against carcinogenesis stems from the considerably lower rates of breast cancer cases in Asian countries compared to Western populations, and the increase in cancer prevalence along with migration of Asian women to the Western world and adoption of western dietary habits (Peeters et al., 2003; Verheus et al., 2007; Hedelin et al., 2008; Goodman et al., 2009; Lee et al., 2009; Magne Nde et al., 2015). The health benefits inherent for Asian region are attributed to the traditionally high intake of soy foods containing plenty of phytoestrogens, isoflavones (Peeters et al., 2003; Verheus et al., 2007; Hedelin et al., 2008; Taylor et al., 2009).

Flavonoids are polyphenolic substances found in different plant-origin food items and comprising more than 5,000 different compounds, divided to flavones (apigenin, luteolin), flavonols (quercetin, kaempferol, myricetin), flavanones (hesperetin, naringenin), flavanols or catechins (catechin, epicatechin, epicatechin 3-gallate, epigallocatechin, epigallocatechin 3-gallate, gallocatechin), isoflavones (genistein, daidzein, glycitein, biochanin A, formononetin) and anthocyanidins (Adebamowo et al., 2005; Zhang et al., 2009; Hui et al., 2013; Sak, 2014). The anticancer action of flavonoids has been a tempting research topic for recent decades and different activities,

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including antioxidant, antiinflammatory, antiproliferative, cytotoxic, antiangiogenic, and antimetastatic properties have been described for various flavonoids in numerous *in vitro* and *in vivo* experiments (Bosetti et al., 2005; Hui et al., 2013). Therefore, it is probable that cancer preventive and suppressive action of these plant secondary metabolites is derived from a variety of biological mechanisms affecting several biochemical pathways involved in tumorigenesis.

In the current review article, the epidemiological data about intake of flavonoids on breast cancer risk were compiled from literary sources, comprising the information on both the dietary consumption as well as biomarkers estimation (in plasma, serum, urine). For this aim, a PubMed search was carried out for articles published only in English language up to December 10th 2016 by using the following terms: "epidemiology" (or "epidemiological"), "cancer" (or "carcinogenesis", "tumor", "tumorigenesis"), and "flavonoid" (or "flavonoids"). All studies performed with breast cancers were further selected and references of extracted papers were carefully examined for identification of additional articles relevant for including in the current work. Moreover, both the case-control studies as well as prospective cohort studies were involved. These data are presented in Tables 1-3 and are further discussed in the following subsections.

Dietary intake of flavonoids and breast cancer risk

Summaries of epidemiological data measured by case-control and prospective cohort study design on associations between dietary flavonoids intake and breast cancer risk are presented in Tables 1 and 2, respectively. Fink (2007) indicated in a case-control study with American population that an increased consumption of total flavonoids, flavones, flavonols and flavanols, but not flavanones and anthocyanidins, was associated with a decreased breast cancer risk that was restricted only to postmenopausal (not premenopausal) women, whereas estrogen receptor (ER) and progesterone receptor (PR) status of tumor did not modify the findings. These outcomes were compatible with the results of two previous case-control studies conducted in Italy and Greece reporting a decrease in breast cancer risk with increasing intake of flavones (Peterson et al., 2003; Bosetti et al., 2005) and flavonols (Bosetti et al., 2005), but not other flavonoid subclasses, including flavanones, flavanols and anthocyanidins (Peterson et al., 2003; Bosetti et al., 2005). Moreover, the more recent findings of Torres-Sanchez (2009) in Mexican population also confirmed the protective effect of high dietary consumption of flavones and flavonols against breast cancer, especially among postmenopausal women (Table 1).

Nevertheless, the results from prospective cohort studies were not so promising concerning the chemopreventive activities of flavonoids. Indeed, no protective effects against overall breast tumorigenesis were shown for increased intake of total flavonoids in different populations (American, Dutch, Finnish) or stratifying cases by menopausal or hormone receptor (ER/PR) status (Knekt et al., 1997; Goldbohm et al., 1998; Knekt et al., 2002; Wang et al., 2009; Zamora-Ros et al., 2013; Wang et al., 2014; Pantavos et al., 2015). These findings were similar also for flavonoid subgroups, i.e. for flavones (Zamora-Ros et al., 2013), flavonols (Goldbohm et al., 1998; Knekt et al., 2002; Adebamowo et al., 2005; Zamora-Ros et al., 2013; Wang et al., 2014), flavanones (Knekt et al., 2002; Zamora-Ros et al., 2013; Wang et al., 2014), flavanols (Arts et al., 2002; Zamora-Ros et al., 2013; Wang et al., 2014), and anthocyanidins (Zamora-Ros et al., 2013). However, in a recent prospective cohort study, Touvier (2013) still described an inverse association between an increased consumption of total flavonoids, flavonols and flavanols and breast cancer risk in French non-to-low alcohol drinkers, although the number of cases (59) was rather small. Somewhat surprisingly, a positive association of total flavonoids, flavanols and anthocyanidins with breast cancer risk was found in this work for women with moderate-to-heavy alcohol intake indicating that some subclasses of polyphenols can possibly elevate the susceptibility to mammary tumorigenesis among women with high daily alcohol use. The possibility can still not be excluded that these findings reflect the well-known deleterious action of alcohol on breast carcinogenesis (Table 2).

The situation seems to be somewhat more delineated in the case of isoflavones. The findings of several case-control studies (Horn-Ross et al., 2001; Peterson et al., 2003; Bosetti et al., 2005; Fink et al., 2007; Cotterchio et al., 2008; Ward et al., 2010) and prospective cohort studies (Horn-Ross et al., 2002; Keinan-Boker et al., 2004; Touillaud et al., 2006; Hedelin et al., 2008; Travis et al., 2008; Zamora-Ros et al., 2013; Wang et al., 2014) demonstrated no associations (overall or stratifying by menopausal status) between isoflavone intake and breast cancer risk in different western populations (American, Canadian, Dutch, English, French, Greek, Italian, Swedish) where the habitual consumption of soy foods is rather low (Tables 1 and 2). It can be hypothesized that this intake level is probably too low to reveal any associations and in line with this assumption, dietary isoflavone intake was indeed related to a decreased breast cancer incidence in Asian countries with remarkably higher soy foods intake. In this way, modest inverse associations were observed in several case-control studies performed with Chinese (Zhang et al., 2009; Zhang et al., 2010; Zhu et al., 2011; Li et al., 2013), Japanese (Hirose et al., 2005; Iwasaki et al., 2008; Iwasaki et al., 2009a), Korean (Cho et al., 2010), Japanese Brazilian (Iwasaki et al., 2009a), Asian American (Wu et al., 2002) and South Asian women living in England (dos Santos Silva et al., 2004), and also in prospective cohort studies conducted with Chinese (Lee et al., 2009), Japanese (Yamamoto et al., 2003; Wada et al., 2013), Singapore Chinese (Wu et al., 2008), and Japanese American women (Morimoto et al., 2014). Further stratification of these results by menopausal status still revealed inconclusive outcomes: some studies showing protective effects of isoflavones only in premenopausal women (54-56% reduction in cancer risk) (Hirose et al., 2005; Lee et al., 2009; Zhang et al., 2010), some works restricting this advantageous action to postmenopausal women (26-68% reduction in cancer risk) (Yamamoto et al., 2003; Wu et al., 2008; Cho et al., 2010; Zhu et al.,

Table 1. Epidemiological Case-Control Studies on Dietary Intake of Flavonoids and Breast Cancer Risk

Flavonoid subclass	Certain compound	Study[a]	Population	Controls[b]	Meno-pausal status	Cases/ controls	Intake comparison (low vs high, mg/day)[c]	Multivariate-adjusted OR/RR/HR[d]	P for trend[e]	Comments[f]	Reference
Flavonoids		LIBCSP	American	PB		1434/1440	0-34.5 vs ≥343.1 (Q5)	0.88 (0.69-1.12)	0.14	NA	Fink et al., 2007
Flavonoids		LIBCSP	American	PB	Pre-	457/487	0-34.5 vs ≥343.1 (Q5)	1.12 (0.72-1.74)	0.95	NA	Fink et al., 2007
Flavonoids		LIBCSP	American	PB	Post-	977/953	0-34.5 vs ≥343.1 (Q5)	0.75 (0.56-1.01)	0.05*	No effect modification by ER/PR status	Fink et al., 2007
Flavones		LIBCSP	American	PB		1434/1440	0-0.04 vs ≥0.22 (Q5)	0.73 (0.57-0.93)	0.004*	NA	Fink et al., 2007
Flavones			Greek			820/1548	0.3 vs 1.1 (Q5)	0.87 (0.77-0.97)	0.02*	NA	Peterson et al., 2003
Flavones			Italian	HB		2569/2588	(Q5)	0.81 (0.66-0.98)	0.02*	NA	Bosetti et al., 2005
Flavones			Mexican	HB		141/141	0.1-1.6 vs 4.0-7.4 (T3)	0.60 (0.27-1.37)	0.241	NA	Torres-Sanchez et al., 2009
Flavones		LIBCSP	American	PB	Pre-	457/487	0-0.04 vs ≥0.22 (Q5)	1.07 (0.70-1.65)	0.94	NA	Fink et al., 2007
Flavones			Mexican	HB	Pre-	68/69	0.1-1.6 vs 4.0-7.4 (T3)	0.49 (0.19-1.29)	0.152	NA	Torres-Sanchez et al., 2009
Flavones		LIBCSP	American	PB	Post-	977/953	0-0.04 vs ≥0.22 (Q5)	0.61 (0.45-0.83)	<0.001*	No effect modification by ER/PR status	Fink et al., 2007
Flavones			Mexican	HB	Post-	70/71	0.1-1.6 vs 4.0-7.4 (T3)	0.29 (0.10-0.82)	0.025*	NA	Torres-Sanchez et al., 2009
Flavonols		LIBCSP	American	PB		1434/1440	0-3.7 vs ≥15.2 (Q5)	0.75 (0.59-0.95)	0.05*	NA	Fink et al., 2007
Flavonols			Greek			820/1548	9.7 vs 30.6 (Q5)	0.91 (0.78-1.06)	0.22	NA	Peterson et al., 2003
Flavonols			Italian	HB		2569/2588	(Q5)	0.80 (0.66-0.98)	0.06	NA	Bosetti et al., 2005
Flavonols			Mexican	HB		141/141	2.3-26.0 vs 36.8-72.0 (T3)	0.48 (0.21-1.08)	0.08	NA	Torres-Sanchez et al., 2009
Flavonols		LIBCSP	American	PB	Pre-	457/487	0-3.7 vs ≥15.2 (Q5)	1.38 (0.88-2.15)	0.92	NA	Fink et al., 2007
Flavonols			Mexican	HB	Pre-	68/69	2.3-26.0 vs 36.8-72.0 (T3)	0.49 (0.19-1.23)	0.126	NA	Torres-Sanchez et al., 2009
Flavonols		LIBCSP	American	PB	Post-	977/953	0-3.7 vs ≥15.2 (Q5)	0.54 (0.40-0.73)	<0.001*	No effect modification by ER/PR status	Fink et al., 2007
Flavonols			Mexican	HB	Post-	70/71	2.3-26.0 vs 36.8-72.0 (T3)	0.21 (0.07-0.60)	0.004*	NA	Torres-Sanchez et al., 2009
Flavanones		LIBCSP	American	PB		1434/1440	0-3.1 vs ≥40.4 (Q5)	0.89 (0.70-1.12)	0.64	NA	Fink et al., 2007
Flavanones			Greek			820/1548	9.1 vs 67.1 (Q5)	0.96 (0.87-1.07)	0.44	NA	Peterson et al., 2003
Flavanones			Italian	HB		2569/2588	(Q5)	0.95 (0.79-1.15)	0.49	NA	Bosetti et al., 2005
Flavanones		LIBCSP	American	PB	Pre-	457/487	0-3.1 vs ≥40.4 (Q5)	0.80 (0.53-1.21)	0.34	NA	Fink et al., 2007
Flavanones		LIBCSP	American	PB	Post-	977/953	0-3.1 vs ≥40.4 (Q5)	1.00 (0.75-1.34)	0.87	No effect modification by ER/PR status	Fink et al., 2007
Flavanols		LIBCSP	American	PB		1434/1440	0-5.1 vs ≥264.2 (Q5)	0.85 (0.67-1.08)	0.17	NA	Fink et al., 2007
Flavanols			Greek			820/1548	9.0 vs 45.2 (Q5)	0.93 (0.78-1.11)	0.43	NA	Peterson et al., 2003
Flavanols			Italian	HB		2569/2588	(Q5)	0.86 (0.71-1.05)	0.26	NA	Bosetti et al., 2005
Flavanols			Mexican	HB		141/141	0.2-5.9 vs 10.6-4.59 (T3)	0.80 (0.38-1.70)	0.561	NA	Torres-Sanchez et al., 2009
Flavanols		LIBCSP	American	PB	Pre-	457/487	0-5.1 vs ≥264.2 (Q5)	1.21 (0.78-1.86)	0.87	NA	Fink et al., 2007
Flavanols			Mexican	HB	Pre-	68/69	0.2-5.9 vs 10.6-45.9 (T3)	1.22 (0.48-3.08)	0.679	NA	Torres-Sanchez et al., 2009
Flavanols		LIBCSP	American	PB	Post-	977/953	0-5.1 vs ≥264.2 (Q5)	0.74 (0.55-0.99)	0.06	No effect modification by ER/PR status	Fink et al., 2007
Flavanols			Mexican	HB	Post-	70/71	0.2-5.9 vs 10.6-45.9 (T3)	0.63 (0.25-1.62)	0.349	NA	Torres-Sanchez et al., 2009

Table 1. Continued

Flavonoid subclass	Certain compound	Studya	Population	Controlsb	Meno-pausal status	Cases/ controls	Intake comparison (low vs high, mg/day)c	Multivariate-adjusted OR/RR/ HRd	P for trende	Commentsf	Reference
Isoflavones		LIBCSP	American	PB		1434/1440	0-0.31 vs ≥7.63 (Q5)	0.95 (0.74-1.22)	0.31	NA	Fink et al., 2007
Isoflavones			American (multiethnic, non-Asian)	PB		1272/1610	<1.048 vs ≥2.775 (Q4)	1.0 (0.79-1.3)		No effect modification by ethnicity (African American, Latina or White)	Horn-Ross et al., 2001
Isoflavones			Asian-American (multiethnic)	PB		501/594	≤1.79 vs >12.68 /1000 kcal (Q4)	0.61 (0.39-0.97)	0.04*	NA	Wu et al., 2002
Isoflavones		OWDHS	Canadian	PB		3000/3370	0-0.082 vs 1.237-158.983 (Q5)	1.06 (0.87-1.30)		No effect modification by BMI strata (≤25, >25)	Cotterchio et al., 2008
Isoflavones		OWDHS	Canadian	PB		3024/3420	(Q4)	0.81 (0.71-0.94)	<0.01*	Intake in adolescence	Thanos et al., 2006
Isoflavones		EPIC-Norfolk	English	PB		244/938		1.05 (0.90-1.21)	0.54	NA	Ward et al., 2010
Isoflavones			South Asian in England	PB		240/477	<0.125 vs ≥0.470 (Q4)	0.58 (0.33-1.00)	0.08	NA	dos Santos Silva et al., 2004
Isoflavones			Greek			820/1548	0.01 vs 0.8 (Q5)	1.07 (0.97-1.18)	0.17	NA	Peterson et al., 2003
Isoflavones			Italian	HB		2569/2588	(Q5)	1.05 (0.86-1.29)	0.78	NA	Bosetti et al., 2005
Isoflavones			Korean			358/360	<8.5 vs ≥23.7 (Q4)	0.81 (0.48-1.38)	0.823	No effect modification by ER/PR status	Cho et al., 2010
Isoflavones			Japanese	HB		390/390	22.1 vs 69.1 (T3)	0.83 (0.54-1.28)	0.39	No effect modification by ER/PR status	Iwasaki et al., 2009a
Isoflavones			Japanese Brazilian	HB		81/81	4.7 vs 42.8 (T3)	0.25 (0.09-0.68)	<0.01*	No effect modification by ER/PR status	Iwasaki et al., 2009a
Isoflavones			Brazilian (non-Japanese)	HB		379/379	0 vs 15.0 (non- vs consumers)	0.56 (0.35-0.90)	*	No effect modification by ER/PR status	Iwasaki et al., 2009a
Isoflavones			Chinese	HB		295/295	<12.49 vs >35.12 (Q4)	0.52 (0.33-0.85)	0.02*	NA	Li et al., 2013
Isoflavones			Chinese	PB		295/295	<12.49 vs >35.12 (Q4)	0.45 (0.27-0.75)	<0.01*	NA	Li et al., 2013
Isoflavones			Chinese	HB		438/438	<3.26 vs >16.89 (Q4)	0.54 (0.34-0.84)	0.001*	A significant inverse association for women with BMI<25; no effect modification by ER/PR status	Zhang et al., 2010
Isoflavones			Chinese	HB		183/192	<7.56 vs >28.83 (Q4)	0.42 (0.22-0.80)	0.031*	A significant inverse association for ER+PR+ (not for ER-PR-, ER+PR- or ER-PR+) tumors	Zhu et al., 2011
Isoflavones			Chinese	HB		/1009	<7.78 vs >25.40 (Q4)		*	No effect modification by ER/PR status	Zhang et al., 2009
Isoflavones		LIBCSP	American	PB	Pre-	457/487	0-0.31 vs ≥7.63 (Q5)	1.14 (0.76-1.72)	0.56	NA	Fink et al., 2007
Isoflavones			American (multiethnic, non-Asian)	PB	Pre-	398/471	<1.048 vs ≥2.775 (Q4)	1.2 (0.75-2.0)		NA	Horn-Ross et al., 2001

Table 1. Continued

Flavonoid subclass	Certain compound	Studya	Population	Controlsb	Meno-pausal status	Cases/ controls	Intake comparison (low vs high, mg/day)c	Multivariate-adjusted OR/RR/ HRd	P for trende	Commentsf	Reference
Isoflavones		OWDHS	Canadian	PB	Pre-	930/1211	0-0.082 vs 1.237-158.983 (Q5)	0.96 (0.69-1.33)		No effect modification by BMI strata (≤25, >25)	Cotterchio et al., 2008
Isoflavones			German	PB	Pre-	278/666	(Q4)	0.85 (0.54-1.33)	0.229	NA	Linseisen et al., 2004
Isoflavones			Korean		Pre-	358/360	<8.5 vs ≥23.7 (Q4)	1.36 (0.64-2.91)	0.209	No effect modification by ER/PR status	Cho et al., 2010
Isoflavones		HERPACC	Japanese	HB	Pre-	79/414	7.61 vs 18.47 /1000 kcal (T3)	0.44 (0.22-0.89)	0.02*	NA	Hirose et al., 2005
Isoflavones			Japanese	HB	Pre-	178/137	22.1 vs 69.1 (T3)	1.35 (0.72-2.54)	0.41	No effect modification by ER/PR status	Iwasaki et al., 2009a
Isoflavones			Japanese Brazilian	HB	Pre-	25/24	8.0 vs 35.0 (two medians)	0.17 (0.03-0.84)	*	NA	Iwasaki et al., 2009a
Isoflavones			Brazilian (non-Japanese)	HB	Pre-	161/145	0 vs 15.0 (non- vs consumers)	0.54 (0.26-1.13)		NA	Iwasaki et al., 2009a
Isoflavones			Chinese	HB	Pre-	306/295	(Q4)	0.46 (0.26-0.82)	<0.001*	NA	Zhang et al., 2010
Isoflavones			Chinese	HB	Pre-	/671	<7.78 vs >25.40 (Q4)		*	No effect modification by ER/PR status	Zhang et al., 2009
Isoflavones			Chinese	HB	Pre-	183/192	<7.56 vs >28.83 (Q4)	0.66 (0.31-1.07)		NA	Zhu et al., 2011
Isoflavones		LIBCSP	American	PB	Post-	977/953	0-0.31 vs ≥7.63 (Q5)	1.02 (0.76-1.38)	0.72	No effect modification by ER/PR status	Fink et al., 2007
Isoflavones			American (multiethnic, non-Asian)	PB	Post-	826/1077	<1.048 vs ≥2.775 (Q4)	0.96 (0.71-1.3)		NA	Horn-Ross et al., 2001
Isoflavones		OWDHS	Canadian	PB	Post-	2067/2154	0-0.082 vs 1.237-158.983 (Q5)	1.09 (0.83-1.41)		No effect modification by BMI strata (≤25, >25)	Cotterchio et al., 2008
Isoflavones			Chinese	HB	Post-	132/143	(Q4)	0.66 (0.30-1.44)	0.281	NA	Zhang et al., 2010
Isoflavones			Korean		Post-	358/360	<8.5 vs ≥23.7 (Q4)	0.33 (0.15-0.72)	0.016*	Inverse association for women with ER+PR+ (not ER-PR-) tumor	Cho et al., 2010
Isoflavones		HERPACC	Japanese	HB	Post-	88/440	8.69 vs 22.26 /1000 kcal (T3)	0.58 (0.30-1.10)	0.09	NA	Hirose et al., 2005
Isoflavones			Japanese	HB	Post-	212/253	22.1 vs 69.1 (T3)	0.62 (0.38-1.01)	0.06	No effect modification by ER/PR status	Iwasaki et al., 2009a
Isoflavones			Japanese Brazilian	HB	Post-	56/57	8.0 vs 35.0 (two medians)	0.84 (0.37-1.92)		NA	Iwasaki et al., 2009a
Isoflavones			Brazilian (non-Japanese)	HB	Post-	218/234	0 vs 15.0 (non- vs consumers)	0.58 (0.33-1.03)		NA	Iwasaki et al., 2009a
Isoflavones			Chinese	HB	Post- or peri-	183/192	<7.56 vs >28.83 (Q4)	0.57 (0.29-0.83)	*	NA	Zhu et al., 2011
Isoflavones			Chinese	HB	Post-	/338	<7.78 vs >25.40 (Q4)		*	No effect modification by ER/PR status	Zhang et al., 2009

Table 1. Continued

Flavonoid subclass	Certain compound	Studya	Population	Controlsb	Meno-pausal status	Cases/ controls	Intake comparison (low vs high, mg/day)c	Multivariate-adjusted OR/RR/ HRd	P for trende	Commentsf	Reference
Isoflavones	Genistein		American (multiethnic, non-Asian)	PB		1272/1610	<0.480 vs ≥1.440 (Q4)	0.92 (0.72-1.2)		NA	Horn-Ross et al., 2001
Isoflavones	Genistein	EPIC-Norfolk	English	PB		244/938		1.04 (0.90-1.19)	0.63	NA	Ward et al., 2010
Isoflavones	Genistein		South Asian in England	PB		240/477	<0 078 vs ≥.0232 (Q4)	0.62 (0.36-1.06)	0.1	NA	dos Santos Silva et al., 2004
Isoflavones	Genistein	JPHC	Japanese	PB		144/288	(Q4)	0.58 (0.29-1.18)	0.21	NA	Iwasaki et al., 2008
Isoflavones	Genistein		Chinese	HB		295/295	<8.46 vs >25.44 (Q4)	0.34 (0.19-0.60)	<0.01*	NA	Li et al., 2013
Isoflavones	Genistein		Chinese	PB		295/295	<8.46 vs >25.44 (Q4)	0.28 (0.15-0.52)	<0.01*	NA	Li et al., 2013
Isoflavones	Genistein		Chinese	HB		/1009	<4.27 vs >14.18 (Q4)		*	No effect modification by ER/PR status	Zhang et al., 2009
Isoflavones	Genistein		German	PB	Pre-	278/666	(Q4)	0.47 (0.29-0.74)	0.002*	NA	Linseisen et al., 2004
Isoflavones	Genistein	JPHC	Japanese	PB	Pre-	59/118	(Q4)	0.62 (0.21-1.84)	0.43	NA	Iwasaki et al., 2008
Isoflavones	Genistein		Chinese	HB	Pre-	/671	<4.27 vs >14.18 (Q4)		*	No effect modification by ER/PR status	Zhang et al., 2009
Isoflavones	Genistein	JPHC	Japanese	PB	Post-	80/160	(Q4)	0.52 (0.19-1.42)	0.31	NA	Iwasaki et al., 2008
Isoflavones	Genistein		Chinese	HB	Post-	/338	<4.27 vs >14.18 (Q4)		*	No effect modification by ER/PR status	Zhang et al., 2009
Isoflavones	Daidzein		American (multiethnic, non-Asian)	PB		1272/1610	<0.473 vs ≥1.223 (Q4)	1.1 (0.85-1.4)		NA	Horn-Ross et al., 2001
Isoflavones	Daidzein	EPIC-Norfolk	English	PB		244/938		1.03 (0.89-1.18)	0.7	NA	Ward et al., 2010
Isoflavones	Daidzein		German	PB	Pre-	278/666	(Q4)	0.62 (0.40-0.95)	0.065	NA	Linseisen et al., 2004
Isoflavones	Daidzein		South Asian in England	PB		240/477	<0 078 vs ≥.0232 (Q4)	0.57 (0.33-0.99)	0.09	NA	dos Santos Silva et al., 2004
Isoflavones	Daidzein	JPHC	Japanese	PB		144/288	(Q4)	0.67 (0.33-1.39)	0.34	NA	Iwasaki et al., 2008
Isoflavones	Daidzein		Chinese	HB		295/295	<6.33 vs >19.47 (Q4)	0.38 (0.22-0.64)	<0.01*	NA	Li et al., 2013
Isoflavones	Daidzein		Chinese	PB		295/295	<6.33 vs >19.47 (Q4)	0.32 (0.18-0.56)	<0.01*	NA	Li et al., 2013
Isoflavones	Daidzein		Chinese	HB		/1009	<2.98 vs >9.76 (Q4)		*	No effect modification by ER/PR status	Zhang et al., 2009
Isoflavones	Daidzein	JPHC	Japanese	PB	Pre-	59/118	(Q4)	0.67 (0.22-2.03)	0.53	NA	Iwasaki et al., 2008
Isoflavones	Daidzein		Chinese	HB	Pre-	/671	<2.98 vs >9.76 (Q4)		*	No effect modification by ER/PR status	Zhang et al., 2009
Isoflavones	Daidzein	JPHC	Japanese	PB	Post-	80/160	(Q4)	0.64 (0.23-1.72)	0.43	NA	Iwasaki et al., 2008
Isoflavones	Daidzein		Chinese	HB	Post-	/338	<2.98 vs >9.76 (Q4)		*	No effect modification by ER/PR status	Zhang et al., 2009

Table 1. Continued

Flavonoid subclass	Certain compound	Studya	Population	Controlsb	Meno-pausal status	Cases/ controls	Intake comparison (low vs high, mg/ day)c	Multivariate-adjusted OR/ RR/HRd	P for trende	Commentsf	Reference
Isoflavones	Biochanin A		American (multiethnic, non-Asian)	PB		1272/1610	<0.022 vs ≥0.083 (Q4)	1.2 (0.85-1.5)		NA	Horn-Ross et al., 2001
Isoflavones	Biochanin A	EPIC-Norfolk	English	PB		244/938		1.10 (0.90-1.34)	0.36	NA	Ward et al., 2010
Isoflavones	Biochanin A		German	PB	Pre-	278/666	(Q4)	0.85 (0.53-1.38)	0.747	NA	Linseisen et al., 2004
Isoflavones	Formononetin		American (multiethnic, non-Asian)	PB		1272/1610	<0.009 vs ≥0.040 (Q4)	1.2 (0.96-1.5)		NA	Horn-Ross et al., 2001
Isoflavones	Formononetin	EPIC-Norfolk	English	PB		244/938		0.94 (0.81-1.09)	0.44	NA	Ward et al., 2010
Isoflavones	Formononetin		German	PB	Pre-	278/666	(Q4)	1.14 (0.72-1.82)	0.395	NA	Linseisen et al., 2004
Isoflavones	Glycitein	EPIC-Norfolk	English	PB		244/938		0.96 (0.80-1.14)	0.63	NA	Ward et al., 2010
Isoflavones	Glycitein		Chinese	HB		295/295	<0.38 vs >1.46 (Q4)	0.66 (0.40-1.08)	0.12	NA	Li et al., 2013
Isoflavones	Glycitein		Chinese	PB		295/295	<0.38 vs >1.46 (Q4)	0.55 (0.33-0.92)	0.02*	NA	Li et al., 2013
Isoflavones	Glycitein		Chinese	HB		/1009	<1.19 vs >6.32 (Q4)		*	No effect modification by ER/PR status	Zhang et al., 2009
Isoflavones	Glycitein		Chinese	HB	Pre-	/671	<1.19 vs >6.32 (Q4)		*	No effect modification by ER/PR status	Zhang et al., 2009
Isoflavones	Glycitein		Chinese	HB	Post-	/338	<1.19 vs >6.32 (Q4)		*	No effect modification by ER/PR status	Zhang et al., 2009
Isoflavones	Equol	EPIC-Norfolk	English	PB		244/938		1.04 (0.86-1.26)	0.7	NA	Ward et al., 2010
Anthocyanidins		LIBCSP	American	PB		1434/1440	0-0.04 vs ≥4.20 (Q5)	0.91 (0.72-1.15)	0.27	NA	Fink et al., 2007
Anthocyanidins			Greek	Case-control		820/1548	5.1 vs 81.4 (Q5)	0.94 (0.81-1.09)	0.39	NA	Peterson et al., 2003
Anthocyanidins			Italian	HB		2569/2588	(Q5)	1.09 (0.87-1.36)	0.38	NA	Bosetti et al., 2005
Anthocyanidins		LIBCSP	American	PB	Pre-	457/487	0-0.04 vs ≥4.20 (Q5)	1.08 (0.71-1.63)	0.81	NA	Fink et al., 2007
Anthocyanidins		LIBCSP	American	PB	Post-	977/953	0-0.04 vs ≥4.20 (Q5)	0.85 (0.64-1.14)	0.23	No effect modification by ER/PR status	Fink et al., 2007

[a], EPIC; The European Prospective Investigation into Cancer and Nutrition; HERPACC, The Hospital-Based Epidemiologic Research Program at Aichi Cancer Center; JPHC, The Japan Public Health Center-based prospective study; LIBCSP, The Long Island Breast Cancer Study Project; OWDHS; The Ontario Women`s Diet and Health Study; [b], HB; hospital-based; PB, population-based; [c], T3; tertiles; Q4, quartiles; Q5, quintiles; [d]OR, odds ratio; RR, relative risk; HR, hazard ratio; [e]Statistically significant effects (p for trend <0.05) are marked by asterisk; [f]ER, estrogen receptor; PR, progesterone receptor; NA, not applicable

2011; Wada et al., 2013) and others demonstrating the benefits for both menopausal strata (Zhang et al., 2009) (Tables 1 and 2). However, Linseisen (2004) suggested an association of dietary intake of two isoflavones, genistein and daidzein (but not total isoflavones), with a decreased breast cancer risk also in premenopausal German women despite a very low consumption of these compounds among German (0.15-0.16 mg/day) compared to Asian population (10-30 mg/day) (Tables 1). The apparent protective effect of (high) isoflavone intake against breast carcinogenesis in premenopausal women can involve a decrease in serum estradiol level, suppression of gonadotropins surge in midcycle and lengthening the menstrual cycle (Zhang et al., 2010).

Besides the apparently essential role of daily amount of dietary isoflavone intake, also the timing of consumption of soy foods seems to be crucial. Indeed, Thanos (2006) suggested that higher intake of isoflavones during adolescence was related to significantly decreased risk of breast cancer among adult Canadian women (Table 1).

Biomarkers of flavonoids and breast cancer risk

Estimation of urinary and plasma/serum metabolites of flavonoids could potentially complement the epidemiological findings obtained from assessment of dietary intake by adding the bioavailability dimension of these compounds. The data about relationships between biomarkers and breast cancer risk are presented in Table 3. There were no statistically significant associations found for the level of urinary flavonols and flavanones or urinary and plasma flavanols with breast cancer risk in either Chinese or Japanese populations, irrespective of the menopausal status of women (Dai et al., 2002; Iwasaki et al., 2010; Luo et al., 2010) (Table 3). However, current results about relationships of urinary and circulating biomarkers of isoflavones and their metabolites with breast cancer incidence are still inconclusive and somewhat controversial. In this way, Dai (2002) reported about two-fold reduction in breast cancer risk in Chinese women with the highest versus lowest urinary excretion of both total isoflavones as well as genistein, daidzein, glycitein and their various metabolites, confirming the previous findings that rich consumption of soy foods might decrease the susceptibility toward breast carcinogenesis. At that, the inverse association between isoflavone excretion and cancer risk was somewhat stronger among postmenopausal women being even more evident among overweight females (Dai et al., 2002; Dai et al., 2003). Similarly, Zheng (1999) reported about half of breast cancer risk in Chinese women with the highest urinary excretion levels of total or individual isoflavones (genistein, daidzein, glycitein), although these results did not reach statistical significance probably because of a small sample size. Goodman (2009) described a decreased risk of breast cancer in postmenopausal Japanese American women with higher urinary excretion of daidzein and Ingram (1997) indicated almost four-fold reduction in breast tumor incidence in Australian women with high urinary levels of equol, a metabolite produced from daidzein. Furthermore, Lampe (2007) observed a remarkable reduction in the risk of both fibrocystic breast conditions as well as mammary cancer among Chinese women with high plasma concentrations of genistein and daidzein suggesting the anticancer effects of isoflavones already in early tumorigenesis. Reduction of breast cancer risk with increasing plasma levels of genistein (but not daidzein) was shown also among Japanese (Iwasaki et al., 2008) and Dutch women (Verheus et al., 2007) (Table 3).

On the contrary, Grace (2004) reported that high exposure to various isoflavones (genistein, daidzein, equol) exhibited even a positive relationship with breast cancer risk by increasing tumor incidence among English women. Although Ward (2008) demonstrated a marginal elevation of breast cancer risk with higher urinary concentrations of total isoflavones, being restricted to pre- and perimenopausal females, analysis by individual compounds (genistein, daidzein, glycitein) did not follow this trend. No considerable association of breast carcinogenesis was found also with urinary excretion of genistein in postmenopausal Dutch women in a prospective study design (den Tonkelaar et al., 2001) (Table 3).

Some reasons for inconsistencies

The above described inconsistencies in associations between intake of flavonoids and breast cancer risk may be explained by several possible reasons. Comparison of different works is complicated due to the variation in estimation of exposure to these polyphenolic compounds as some investigations have assessed dietary intake and others measured biological markers. Evaluation through dietary consumption and measuring daily intake levels of flavonoids has been limited and difficult primarily because of lack of food composition tables (den Tonkelaar et al., 2001; Peeters et al., 2003; Grace et al., 2004; Fink et al., 2007; Cotterchio et al., 2008; Hui et al., 2013; Touvier et al., 2013). Quantitative estimation of dietary consumption has been feasible only since 2003 when the US Department of Agriculture (USDA) released the analytical database for the content of five subclasses of flavonoids (flavones, flavonols, flavanones, flavanols and anthocyanidins) in selected food items; food composition data for isoflavones was available one year earlier, i.e. in 2002 (Peterson et al., 2003; Cotterchio et al., 2008; Hui et al., 2013). Recently, also the Phenol-Explorer database was made public to provide detailed composition data for subgroups of flavonoids (Touvier et al., 2013). However, current dietary assessment tools and information about intake of flavonoids are still rather incomplete as new products are introduced to the market and some food items find nontraditional applications (for instance, soy bars) (Fink et al., 2007; Nagata, 2010; Hui et al., 2013; Morimoto et al., 2014). In particular, intake of isoflavones can be underestimated, especially in populations with low habitual consumption of soy foods where addition of soy to processed foods may be unlisted (Trock et al., 2006; Cotterchio et al., 2008). Also, use of soy and soy components but also other herbal supplements as food additives raises further questions and is needed to take into account in future analyses (Linseisen et al., 2004; Zamora-Ros et al., 2013; Morimoto et al., 2014). Moreover, variations in flavonoid intakes between different studies

Table 2. Epidemiological Prospective Cohort Studies on Dietary Intake of Flavonoids and Breast Cancer Risk

Flavonoid subclass	Certain compound	Study[a]	Population	Median follow-up (years)	Meno-pausal status in baseline	Cases/ cohort	Intake comparison (low vs high, mg/day)[b]	Multivariate-adjusted OR/RR/HR[c]	P for trend[d]	Comments[e]	Reference
Flavonoids		WHS	American	11.5		1351/38408	(Q5)	1.03 (0.85-1.25)	0.79	NA	Wang et al., 2009
Flavonoids		EPIC	Women from ten European countries	11.5		11576/334850	<176.0 vs >654.0 (Q5)	0.97 (0.90-1.04)	0.591	No effect modification by ER/PR status	Zamora-Ros et al., 2013
Flavonoids		NLCS	Dutch	4.3		605/3123	13.5 vs 44.6 (Q5)	1.02 (0.72-1.44)	0.74	NA	Goldbohm et al., 1998
Flavonoids		FMC	Finnish	24		87/9959	<2.4 vs >5.5 (Q4)	0.72 (0.36-1.48)		NA	Knekt et al., 1997
Flavonoids		FMC	Finnish	30		125/4647	8.5 vs 39.5 (Q4)	1.23 (0.72-2.10)	0.53	NA	Knekt et al., 2002
Flavonoids		SU.VI. MAX	French	12.6		59/2011	294.2 vs 631.7 (Q4)	0.35 (0.17-0.75)	0.02*	Non-to-low alcohol users; increased risk in higher drinkers	Touvier et al., 2013
Flavonoids		EPIC	Women from ten European countries	11.5	Pre-	2827/334850	<176.0 vs >654.0 (Q5)	0.98 (0.84-1.15)	0.656	NA	Zamora-Ros et al., 2013
Flavonoids		CPS-II	American	8.5	Post-	2116/56630	≤119 vs >364-2063 (Q5)	0.95 (0.83-1.08)	0.66	No effect modification by ER status	Wang et al., 2014
Flavonoids		EPIC	Women from ten European countries	11.5	Post-	5872/334850	<176.0 vs >654.0 (Q5)	0.96 (0.86-1.06)	0.622	NA	Zamora-Ros et al., 2013
Flavonoids		RS	Dutch	17	Post-	199/3209	18.07 vs 40.46 (T3)	0.93 (0.64-1.34)		NA	Pantavos et al., 2015
Flavones		EPIC	Women from ten European countries	11.5		11576/334850	<1.12 vs >4.88 (Q5)	0.99 (0.91-1.07)	0.729	No effect modification by ER/PR status	Zamora-Ros et al., 2013
Flavones		SU.VI. MAX	French	12.6		152/4141	23.5 vs 30.9 (Q4)	1.53 (1.00-2.36)	0.02*	NA	Touvier et al., 2013
Flavones		EPIC	Women from ten European countries	11.5	Pre-	2827/334850	<1.12 vs >4.88 (Q5)	0.86 (0.73-1.02)	0.162	NA	Zamora-Ros et al., 2013
Flavones		CPS-II	American	8.5	Post-	2116/56630	≤0.6 vs >2.1-8.2 (Q5)	0.88 (0.76-1.01)	0.04*	NA	Wang et al., 2014
Flavones		EPIC	Women from ten European countries	11.5	Post-	5872/334850	<1.12 vs >4.88 (Q5)	1.10 (0.98-1.23)	0.12	NA	Zamora-Ros et al., 2013
Flavonols		EPIC	Women from ten European countries	11.5		11576/334850	<12.8 vs >39.8 (Q5)	0.96 (0.88-1.03)	0.259	No effect modification by ER/PR status	Zamora-Ros et al., 2013
Flavonols		SU.VI. MAX	French	12.6		59/2011	33.0 vs 59.8 (Q4)	0.36 (0.18-0.74)	0.002*	Non-to-low alcohol users	Touvier et al., 2013
Flavonols		NHS II	American	8	Pre-	710/90638	6.8 vs 43.8 (Q5)	1.05 (0.83-1.34)	0.96	NA	Adebamowo et al., 2005
Flavonols		EPIC	Women from ten European countries	11.5	Pre-	2827/334850	<12.8 vs >39.8 (Q5)	0.91 (0.78-1.06)	0.316	NA	Zamora-Ros et al., 2013
Flavonols		CPS-II	American	8.5	Post-	2116/56630	≤8.3 vs >20.8-83.1 (Q5)	0.92 (0.81-1.06)	0.41	No effect modification by ER status	Wang et al., 2014
Flavonols		EPIC	Women from ten European countries	11.5	Post-	5872/334850	<12.8 vs >39.8 (Q5)	1.00 (0.90-1.12)	0.893	NA	Zamora-Ros et al., 2013

Table 2. Continued

Flavonoid subclass	Certain compound	Studya	Population	Median follow-up (years)	Meno-pausal status in baseline	Cases/ cohort	Intake comparison (low vs high, mg/day)b	Multivariate-adjusted OR/RR/HRc	P for trendd	Commentse	Reference
Flavonols	Kaempferol	NLCS	Dutch	4.3		605/3123	2.6 vs 12.9 (Q5)	1.02 (0.72-1.45)	0.286	NA	Goldbohm et al., 1998
Flavonols	Kaempferol	FMC	Finnish	30		125/4647	0.2 vs 0.9 (Q4)	0.87 (0.53-1.41)	0.7	NA	Knekt et al., 2002
Flavonols	Kaempferol	NHS II	American	8	Pre-	710/90638	0.8 vs 12.9 (Q5)	1.01 (0.80-1.27)	0.91	NA	Adebamowo et al., 2005
Flavonols	Myricetin	FMC	Finnish	30		125/4647	0.03 vs 0.20 (Q4)	0.95 (0.57-1.60)	0.63	NA	Knekt et al., 2002
Flavonols	Myricetin	NHS II	American	8	Pre-	710/90638	0.09 vs 2.62 (Q5)	0.99 (0.78-1.26)	0.35	NA	Adebamowo et al., 2005
Flavonols	Quercetin	NLCS	Dutch	4.3		605/3123	8.9 vs 30.8 (Q5)	1.00 (0.70-1.41)	0.957	NA	Goldbohm et al., 1998
Flavonols	Quercetin	FMC	Finnish	30		125/4647	1.8 vs 4.7 (Q4)	0.62 (0.37-1.03)	0.25	NA	Knekt et al., 2002
Flavonols	Quercetin	NHS II	American	8	Pre-	710/90638	5.3 vs 30.1 (Q5)	1.05 (0.83-1.33)	0.81	NA	Adebamowo et al., 2005
Flavanones		EPIC	Women from ten European countries	11.5		11576/334850	<6.2 vs >33.0 (Q5)	0.99 (0.93-1.06)	0.562	No effect modification by ER/PR status	Zamora-Ros et al., 2013
Flavanones		SU.VI.MAX	French	12.6		59/2011	18.6 vs 28.3 (Q4)	1.27 (0.65-2.48)	0.62	Non-to-low alcohol users; no effect modification for higher drinkers	Touvier et al., 2013
Flavanones		EPIC	Women from ten European countries	11.5	Pre-	2827/334850	<6.2 vs >33.0 (Q5)	1.02 (0.89-1.18)	0.283	NA	Zamora-Ros et al., 2013
Flavanones		CPS-II	American	8.5	Post-	2116/56630	≤6.5 vs >34.0-162 (Q5)	1.04 (0.90-1.19)	0.34	No effect modification by ER status	Wang et al., 2014
Flavanones		EPIC	Women from ten European countries	11.5	Post-	5872/334850	<6.2 vs >33.0 (Q5)	1.04 (0.95-1.15)	0.401	NA	Zamora-Ros et al., 2013
Flavanones	Hesperetin	FMC	Finnish	30		125/4647	3.2 vs 26.8 (Q4)	1.08 (0.63-1.86)	0.93	NA	Knekt et al., 2002
Flavanones	Naringenin	FMC	Finnish	30		125/4647	0.9 vs 7.7 (Q4)	1.14 (0.67-1.94)	0.82	NA	Knekt et al., 2002
Flavanols		EPIC	Women from ten European countries	11.5		11576/334850	<18.2 vs >379.8 (Q5)	1.01 (0.93-1.09)	0.856	No effect modification by ER/PR status	Zamora-Ros et al., 2013
Flavanols		SU.VI.MAX	French	12.6		59/2011	61.2 vs 151.5 (Q4)	0.48 (0.22-1.05)	0.02*	Non-to-low alcohol users; increased risk in higher drinkers	Touvier et al., 2013
Flavanols		EPIC	Women from ten European countries	11.5	Pre-	2827/334850	<18.2 vs >379.8 (Q5)	0.96 (0.82-1.13)	0.7	NA	Zamora-Ros et al., 2013
Flavanols		CPS-II	American	8.5	Post-	2116/56630	≤9.0 vs >36.7-410 (Q5)	0.98 (0.86-1.12)	0.56	NA	Wang et al., 2014
Flavanols		IWHS	American	13	Post-	1069/34651	3.6 vs 75.1 (Q5)	1.04 (0.84-1.28)	1	NA	Arts et al., 2002
Flavanols		EPIC	Women from ten European countries	11.5	Post-	5872/334850	<18.2 vs >379.8 (Q5)	1.00 (0.90-1.11)	0.932	NA	Zamora-Ros et al., 2013

Table 2. Continued

Flavonoid subclass	Certain compound	Study[a]	Population	Median follow-up (years)	Meno-pausal status in baseline	Cases/ cohort	Intake comparison (low vs high, mg/ day)[b]	Multivariate-adjusted OR/RR/ HR[c]	P for trend[d]	Comments[e]	Reference
Isoflavones		MEC	American, Hawaiian (multiethnic)	13.7		4769/84450	1.7 vs 29.6 (Q4)	0.96 (0.85-1.08)	0.4	A weak protective association for Japanese American; no effect modification by ER status	Morimoto et al., 2014
Isoflavones		EPIC	Women from ten European countries	11.5		11576/334850	<0.22 vs >1.36 (Q5)	1.00 (0.91-1.10)	0.734	No effect modification by ER/PR status	Zamora-Ros et al., 2013
Isoflavones		EPIC-Oxford	British	7.4		585/37643	<10 vs >20	1.17 (0.79-1.71)	0.36	No effect modification for non-HRT users	Travis et al., 2008
Isoflavones		EPIC-Dutch	Dutch	5.2		280/15555	0.19 vs 0.77 (Q4)	0.98 (0.65-1.48)	0.92	NA	Keinan-Boker et al., 2004
Isoflavones		WLH-Swedish	Swedish	13		1014/45448	(Q4)	0.98 (0.83-1.17)		No effect modification by age strata (<50, ≥50 y)	Hedelin et al., 2008
Isoflavones		TS	Japanese	15.5		172/15607	18.6 vs 70.6 (Q4)	0.67 (0.44-1.03)	0.25	NA	Wada et al., 2013
Isoflavones		SWHS	Chinese	7.4		594/73223	11.23 vs 54.97 (Q5)	0.81 (0.61-1.07)	0.091	NA	Lee et al., 2009
Isoflavones		SCHS	Singapore Chinese			629/35303	<10.6 vs ≥10.6 /1000 kcal	0.82 (0.70-0.97)	0.019*	Strong association for women with >10 y follow-up	Wu et al., 2008
Isoflavones		EPIC	Women from ten European countries	11.5	Pre-	2827/334850	<0.22 vs >1.36 (Q5)	0.94 (0.77-1.16)	0.351	NA	Zamora-Ros et al., 2013
Isoflavones		EPIC-Oxford	British	7.4	Pre-	196/37643	<10 vs >10	1.31 (0.95-1.81)	0.11	NA	Travis et al., 2008
Isoflavones		E3N	French	12	Pre-	402/26868	0.001-0.022 vs 0.036-0.112 (Q4)	1.00 (0.76-1.31)	0.48	NA	Touillaud MS et al 2006 15 2574-6)
Isoflavones		TS	Japanese	15.5	Pre-	38/5926	17.8 vs 68.5 (Q4)	1.52 (0.63-3.65)	0.14	NA	Wada et al., 2013
Isoflavones		SWHS	Chinese	7.4	Pre-	305/73223	11.23 vs 54.97 (Q5)	0.44 (0.26-0.73)	<0.001*	NA	Lee et al., 2009
Isoflavones		SCHS	Singapore Chinese		Pre-	190/35303	<10.6 vs ≥10.6 /1000 kcal	1.04 (0.77-1.40)	0.82	NA	Wu et al., 2008
Isoflavones		CPS-II	American	8.5	Post-	2116/56630	≤0.026 vs >0.093-45.0 (Q5)	1.04 (0.91-1.20)	0.64	No effect modification by ER status	Wang et al., 2014
Isoflavones		MEC	American, Hawaiian (multiethnic)	13.7	Post-	4112/84450	1.7 vs 29.6 (Q4)	0.98 (0.86-1.12)	0.56	NA	Morimoto et al., 2014
Isoflavones		EPIC	Women from ten European countries	11.5	Post-	5872/334850	<0.22 vs >1.36 (Q5)	1.00 (0.87-1.14)	0.702	NA	Zamora-Ros et al., 2013
Isoflavones		EPIC-Oxford	British	7.4	Post-	310/37643	<10 vs >10	0.95 (0.66-1.38)	0.8	NA	Travis et al., 2008
Isoflavones		TS	Japanese	15.5	Post-	134/15264	18.7 vs 70.6 (Q4)	0.52 (0.32-0.85)	0.046*	Stronger inverse association for women with BMI<25, never smokers, drinker	Wada et al., 2013

Table 2. Continued

Flavonoid subclass	Certain compound	Study[a]	Population	Median follow-up (years)	Meno-pausal status in baseline	Cases/ cohort	Intake comparison (low vs high, mg/ day)[b]	Multivariate-adjusted OR/RR/HR[c]	P for trend[d]	Comments[e]	Reference
Isoflavones		SWHS	Chinese	7.4	Post-	289/73223	11.23 vs 54.97 (Q5)	1.09 (0.78-1.52)	0.8	NA	Lee et al., 2009
Isoflavones		SCHS	Singapore Chinese		Post-	439/35303	<10.6 vs ≥10.6 /1000 kcal	0.74 (0.61-0.90)	0.003*	Strong association for women with >10 y follow-up; a significant association for women with BMI>24 (not ≤24); no effect modification by ER/PR status	Wu et al., 2008
Isoflavones	Genistein	CTS	American	2		711/111526	(Q5)	1.0 (0.7-1.3)	0.9	NA	Horn-Ross et al., 2002
Isoflavones	Genistein	WLH -Swedish	Swedish	13		1014/45448	(Q4)	1.01 (0.84-1.20)		No effect modification by age strata (<50, ≥50 y)	Hedelin et al., 2008
Isoflavones	Genistein	JPHC	Japanese	10		179/21852	6.9±2.6 vs 25.3±2.2 (Q4)	0.46 (0.25-0.84)	0.043*	NA	Yamamoto et al., 2003
Isoflavones	Genistein	JPHC	Japanese	10	Pre-	89/21852	(Q4)	0.66 (0.25-1.7)	0.97	NA	Yamamoto et al., 2003
Isoflavones	Genistein	JPHC	Japanese	10	Post-	87/21852	(Q4)	0.32 (0.14-0.71)	0.006*	NA	Yamamoto et al., 2003
Isoflavones	Daidzein	CTS	American	2		711/111526	(Q5)	0.9 (0.7-1.2)	0.6	NA	Horn-Ross et al., 2002
Isoflavones	Daidzein	WLH-Swedish	Swedish	13		1014/45448	(Q4)	1.07 (0.90-1.28)		No effect modification by age strata (<50, ≥50 y)	Hedelin et al., 2008
Isoflavones	Biochanin A	CTS	American	2		711/111526	(Q5)	1.0 (0.8-1.3)	0.7	NA	Horn-Ross et al., 2002
Isoflavones	Formononetin	CTS	American	2		711/111526	(Q5)	1.1 (0.8-1.4)	0.4	NA	Horn-Ross et al., 2002
Anthocyanidins		EPIC	Women from ten European countries	11.5		11576/334850	<12.1 vs >43.6 (Q5)	1.02 (0.94-1.10)	0.56	No effect modification by ER/ PR status	Zamora-Ros et al., 2013
Anthocyanins		SU.VI. MAX	French	12.6		59/2011	24.5 vs 56.9 (Q4)	0.55 (0.23-1.27)	0.08	Non-to-low alcohol users; increased risk in higher drinkers	Touvier et al., 2013
Anthocyanidins		EPIC	Women from ten European countries	11.5	Pre-	2827/334850	<12.1 vs >43.6 (Q5)	1.09 (0.93-1.28)	0.323	NA	Zamora-Ros et al., 2013
Anthocyanidins		CPS-II	American	8.5	Post-	2116/56630	≤5.3 vs >16.1-97.9 (Q5)	0.91 (0.80-1.05)	0.52	No effect modification by ER status	Wang et al., 2014
Anthocyanidins		EPIC	Women from ten European countries	11.5	Post-	5872/334850	<12.1 vs >43.6 (Q5)	1.01 (0.90-1.13)	0.829	NA	Zamora-Ros et al., 2013

[a]CPS-II, The Cancer Prevention Study II Nutrition Cohort; CTS, The California Teachers Study (USA); E3N, Etude Epidemiologique aupres de femmes de la Mutuelle Generale de l´Education Nationale; EPIC, The European Prospective Investigation into Cancer and Nutrition; FMC, The Finnish Mobile Clinic Health Examination Survey; IWHS, The Iowa Women`s Health Study; JPHC, The Japan Public Health Center-based prospective study; MEC, The Multiethnic Cohort Study; NHS II, The Nurses Health Study II; NLCS, The Netherlands Cohort Study; RS, The Rotterdam Study; SCHS, The Singapore Chinese Health Study; SU.VI.MAX, The Supplementation en Vitamines et Mineraux AntioXydants study; SWHS, The Shanghai Women`s Health Study; TS, The Takayama Study; WHS, The Women`s Health Study; WLH, The Scandinavian Women`s Lifestyle and Health Cohort;[b]T3, tertiles; Q4, quartiles; Q5, quintiles; [c]OR, odds ratio; RR, relative risk; HR, hazard ratio; [d]Statistically significant effects (p for trend <0.05) are marked by asterisk; [e]ER, estrogen receptor; HRT, hormone replacement therapy; PR, progesterone receptor; NA, not applicable.

can be explained not only by diverse dietary habits and personal preferences but also by the differences in flavonoid contents in certain food items (Linseisen et al., 2004; Zhang et al., 2010). Indeed, content of flavonoids in food products can substantially vary according to species, differences in cultivars, environmental conditions, geographic location, season, climatic conditions, storage conditions, level of ripeness at the harvest time, but also processing methods and food preparation processes (dos Santos Silva et al., 2004; Grace et al., 2004; Adebamowo et al., 2005; Fink et al., 2007; Iwasaki et al., 2010; Luo et al., 2010). Therefore, the adaptability of USDA flavonoid databases to the diet of European or Asian populations can be somewhat questionable (Bosetti et al., 2005) and possible errors in estimation of exposure to flavonoids through dietary intake must be taken into account in interpreting the association findings.

On the other hand, different findings from Asian and Western populations about relationship between consumption of isoflavones and breast cancer risk suggest that isoflavone intake may still affect mammary carcinogenesis but dose may play a crucial role (Adebamowo et al., 2005; Lampe et al., 2007; Xie et al., 2013). It is conceivable that isoflavone intake has to reach a certain amount (overcome the so-called threshold level) in order to produce benefits and intake of soy foods in Western populations is too low and insufficient to provide enough isoflavones to decrease the risk of breast cancer (Horn-Ross et al., 2001; dos Santos Silva et al., 2004; Bosetti et al., 2005; Lampe et al., 2007; Ward et al., 2008; Wada et al., 2013; Xie et al., 2013). Indeed, the daily intake of isoflavones among women in the United States and Europe is usually less than 3 mg, whereas older adults in China and Japan consume even 25-50 mg of isoflavones per day meaning that higher consumption levels among Western women are far below the lower doses in Asian women (Peeters et al., 2003; Messina et al., 2006; Cotterchio et al., 2008; Messina et al., 2008; Nagata, 2010; Dong and Qin, 2011; Zamora-Ros et al., 2013). Because of this high level and also large variation in soy food intake, Asian populations are ideal settings for estimation of the associations between isoflavone consumption and breast cancer risk (Yamamoto et al., 2003; Iwasaki et al., 2008; Lee et al., 2009; Taylor et al., 2009).

Given the difficulties to detect all flavonoids-containing foods and additives in the diet, the use of biomarkers, such as blood levels or urinary excretion, may provide a more relevant and precise measure to estimate flavonoid consumption than dietary assessment (den Tonkelaar et al., 2001; Verheus et al., 2007; Ward et al., 2008; Luo et al., 2010; Morimoto et al., 2014). Moreover, after intake, flavonoids undergo numerous metabolic conversions in the gastrointestinal tract by intestinal bacteria, as a result of which both parent polyphenols as well as their different conjugates reach circulation and target tissues, and are eventually excreted mainly in urine (Zheng et al., 1999; Dai et al., 2002; Peeters et al., 2003; Lampe et al., 2007; Travis et al., 2008; Luo et al., 2010). It is thus possible that the most abundant compounds in the diet are not necessarily the ones which enter into bloodstream (Touvier et al., 2013). However, currently available food composition databases do not consider the differences in degree of metabolism and absorption of polyphenols that may be a critical factor of exposure to these phytochemicals in understanding their health effects (Lampe et al., 2007; Touvier et al., 2013). Moreover, there can be a large interindividual variation in absorption and excretion of flavonoids after ingestion, depending besides the amount and frequency of intake also on the microbial communities of gut, stress, possible bowel diseases, use of antibiotics (which affect the intestinal microflora), food matrix and background diet, endogenous hormones, or even on genetics and ethnicity (den Tonkelaar et al., 2001; Dai et al., 2002; dos Santos Silva et al., 2004; Kumar et al., 2004; Adebamowo et al., 2005; Trock et al., 2006; Verheus et al., 2007; Hedelin et al., 2008; Luo et al., 2010; Nagata, 2010). Indeed, the interindividual urinary excretion of total isoflavones was shown to vary 16-fold after ingestion of foods rich in soy products and the level of some metabolites can fluctuate even more (Dai et al., 2002). Furthermore, the bioactivities of parent compounds and metabolites can differ. For instance, equol is exclusively the metabolite produced from dietary isoflavone daidzein by certain intestinal bacteria. Only about 30-50 % of individuals are able to generate equol in response to dietary exposure to daidzein, whereas Asian subjects tend to be more likely toward this conversion than Western populations (Keinan-Boker et al., 2004; Linseisen et al., 2004; Lampe et al., 2007; Verheus et al., 2007; Iwasaki et al., 2008; Ward et al., 2008; Cho et al., 2010; Nagata, 2010). This higher prevalence of equol producers among Asian women might add one more explanation also to the beneficial effects of soy foods intake in terms of decreased susceptibility to breast carcinogenesis (Nagata, 2010). At that, equol exerts greater biological activity (including estrogenic action) than daidzein and is a much stronger antioxidant than all other isoflavones; therefore, only subjects who are equol producers experience these benefits (Keinan-Boker et al., 2004; Linseisen et al., 2004; Iwasaki et al., 2008; Cho et al., 2010; Nagata, 2010; Dong and Qin, 2011; Kang et al., 2012).

Although the use of biomarkers (plasma concentrations and urinary excretion) that integrate dietary consumption, metabolism and bioavailability of flavonoids may be more accurate, informative and attractive measure than dietary assessment, it primarily reflects the intake levels of flavonoid-containing foods only over a very short period (for instance, the half-lives of isoflavones in plasma are 6-8 h and almost all are excreted within 24-96 h after ingestion) (Ingram et al., 1997; Zheng et al., 1999; den Tonkelaar et al., 2001; Dai et al., 2002; Peeters et al., 2003; dos Santos Silva et al., 2004; Messina et al., 2006; Lampe et al., 2007; Iwasaki et al., 2008; Goodman et al., 2009). Therefore, recent diet may have a major impact on the levels of urinary polyphenols revealing also a large intraindividual variability within the time of day and timing regarding to meals (Zheng et al., 1999; Dai et al., 2002; Trock et al., 2006; Iwasaki et al., 2008; Iwasaki et al., 2010; Chen et al., 2014). Even though the consumption of flavonoids-containing foods is a personal dietary and

Table 3. Epidemiological Studies on Biomarkers of Flavonoids and Breast Cancer Risk

Flavonoid subclass	Certain compound	Bio-marker	Study[a]	Population	Menopausal status	Cases/ controls	Multivariate-adjusted OR[b]	P for trend[c]	Comments[d]	Reference
Flavonols		Urinary	SWHS	Chinese		353/701	1.04 (0.73-1.48)	0.605	NA	Luo et al., 2010
Flavonols	Kaempferol	Urinary	SWHS	Chinese		353/701	1.11 (0.77-1.60)	0.463	NA	Luo et al., 2010
Flavonols	Quercetin	Urinary	SWHS	Chinese		353/701	1.01 (0.71-1.43)	0.74	NA	Luo et al., 2010
Flavanones	Citrus flavonoids	Urinary	SBCS	Chinese		250/250	1.04 (0.66-1.63)	0.86	NA	Dai et al., 2002
Flavanones	Citrus flavonoids	Urinary	SBCS	Chinese	Pre-	132/132	1.53 (0.77-3.04)	0.27	NA	Dai et al., 2002
Flavanones	Citrus flavonoids	Urinary	SBCS	Chinese	Post-	118/118	0.79 (0.41-1.51)	0.51	NA	Dai et al., 2002
Flavanones	Hesperetin	Urinary	SBCS	Chinese		250/250	0.87 (0.54-1.39)	0.42	NA	Dai et al., 2002
Flavanones	Naringenin	Urinary	SBCS	Chinese		250/250	1.02 (0.66-1.60)	0.92	NA	Dai et al., 2002
Flavanols	(-)-Epicatechin	Plasma	JPHC	Japanese		144/288	0.95 (0.43-2.08)	0.86	NA	Iwasaki et al., 2010
Flavanols	(-)-Epicatechin	Plasma	JPHC	Japanese	Pre-	59/118	1.15 (0.43-3.11)		NA	Iwasaki et al., 2010
Flavanols	(-)-Epicatechin	Plasma	JPHC	Japanese	Post-	80/160	1.11 (0.43-2.84)		NA	Iwasaki et al., 2010
Flavanols	(-)-Epicatechin	Urinary	SWHS	Chinese		353/701	1.01 (0.72-1.40)	0.564	NA	Luo et al., 2010
Flavanols	(-)-Epigallocatechin	Plasma	JPHC	Japanese		144/288	0.90 (0.42-1.96)	0.98	NA	Iwasaki et al., 2010
Flavanols	(-)-Epigallocatechin	Plasma	JPHC	Japanese	Pre-	59/118	1.44 (0.58-3.58)		NA	Iwasaki et al., 2010
Flavanols	(-)-Epigallocatechin	Plasma	JPHC	Japanese	Post-	80/160	0.95 (0.42-2.18)		NA	Iwasaki et al., 2010
Flavanols	(-)-Epigallocatechin	Urinary	SWHS	Chinese		353/701	0.88 (0.62-1.26)	0.344	NA	Luo et al., 2010
Flavanols	(-)-Epicatechin 3-gallate	Plasma	JPHC	Japanese		144/288	1.75 (0.81-3.78)	0.15	NA	Iwasaki et al., 2010
Flavanols	(-)-Epicatechin 3-gallate	Plasma	JPHC	Japanese	Pre-	59/118	1.67 (0.62-4.50)		NA	Iwasaki et al., 2010
Flavanols	(-)-Epicatechin 3-gallate	Plasma	JPHC	Japanese	Post-	80/160	1.91 (0.72-5.07)		NA	Iwasaki et al., 2010
Flavanols	(-)-Epigallocatechin 3-gallate	Plasma	JPHC	Japanese		144/288	1.21 (0.52-2.80)	0.53	NA	Iwasaki et al., 2010
Flavanols	(-)-Epigallocatechin 3-gallate	Plasma	JPHC	Japanese	Pre-	59/118	1.78 (0.66-4.79)		NA	Iwasaki et al., 2010
Flavanols	(-)-Epigallocatechin 3-gallate	Plasma	JPHC	Japanese	Post-	80/160	1.22 (0.50-2.95)		NA	Iwasaki et al., 2010
Isoflavones		Serum	EPIC-Norfolk	English		219/891	1.03 (0.95-1.11)	0.479	No effect modification by ER+ status	Ward et al., 2008
Isoflavones		Urinary	SBCS	Chinese		60/60	0.50 (0.191.31)	0.11	NA	Zheng et al., 1999
Isoflavones		Urinary	SBCS	Chinese		250/250	0.62 (0.39-0.99)	0.04*	NA	Dai et al., 2002
Isoflavones		Urinary	EPIC-Norfolk	English		198/797	1.08 (1.00-1.16)	0.055	No effect modification by ER+ status	Ward et al., 2008
Isoflavones		Urinary	SBCS	Chinese	Pre-	132/132	0.72 (0.36-1.44)	0.33	NA	Dai et al., 2002
Isoflavones		Urinary	EPIC-Norfolk	English	Pre- and peri-		1.30 (1.04-1.64)	0.022*	NA	Ward et al., 2008
Isoflavones		Urinary	SBCS	Chinese	Post-	118/118	0.54 (0.28-1.06)	0.07	NA	Dai et al., 2002
Isoflavones		Urinary	EPIC-Norfolk	English	Post-		1.01 (0.96-1.13)	0.372	NA	Ward et al., 2008
Isoflavones		Urinary	SBCS	Chinese	Post-	117/117	0.46 (0.22-0.95)	0.04*	Significant inverse association only for women with BMI≥25, WHR≥0.84; blood E2>5.73 pg/ml, E1-S≤0.96 ng/ml, SHBG≤81.4 nM	Dai et al., 2003

Table 3. Continued

Flavonoid subclass	Certain compound	Bio-marker	Study[a]	Population	Menopausal status	Cases/ controls	Multivariate-adjusted OR[b]	P for trend[c]	Comments[d]	Reference
Isoflavones	Genistein	Plasma	EPIC Dutch	Dutch		388/388	0.68 (0.47-0.98)	0.07	NA	Verheus et al., 2007
Isoflavones	Genistein	Plasma	JPHC	Japanese		144/288	0.34 (0.16-0.74)	0.02*	NA	Iwasaki et al., 2008
Isoflavones	Genistein	Plasma		Chinese		188/982	0.26 (0.13-0.50)	0.0001*	NA	Lampe et al., 2007
Isoflavones	Genistein	Plasma	JPHC	Japanese	Pre-	59/118	0.14 (0.03-0.69)	0.2	NA	Iwasaki et al., 2008
Isoflavones	Genistein	Plasma	EPIC Dutch	Dutch	Pre- or peri-	87/87	0.80 (0.38-1.69)	0.65	NA	Verheus et al., 2007
Isoflavones	Genistein	Plasma	EPIC Dutch	Dutch	Post-	296/296	0.69 (0.45-1.04)	0.09	NA	Verheus et al., 2007
Isoflavones	Genistein	Plasma	JPHC	Japanese	Post-	80/160	0.36 (0.12-1.12)	0.1	NA	Iwasaki et al., 2008
Isoflavones	Genistein	Serum	EPIC-Norfolk	English		97/187	1.237 (0.976-1.569)	0.077	NA	Grace et al., 2004
Isoflavones	Genistein	Serum	EPIC-Norfolk	English		219/891	1.00 (0.94-1.05)	0.911	No effect modification by ER+ status	Ward et al., 2008
Isoflavones	Genistein	Urinary	EPIC-Norfolk	English		114/219	1.162 (0.973-1.387)	0.097	NA	Grace et al., 2004
Isoflavones	Genistein	Urinary	EPIC-Norfolk	English		198/797	1.01 (0.97-1.05)	0.706	No effect modification by ER+ status	Ward et al., 2008
Isoflavones	Genistein	Urinary	SBCS	Chinese		60/60	0.70 (0.27-1.84)	0.27	NA	Zheng et al., 1999
Isoflavones	Genistein	Urinary	SBCS	Chinese		250/250	0.65 (0.41-1.03)	0.07	NA	Dai et al., 2002
Isoflavones	Genistein	Urinary	MEC	American (multiethnic)	Post-	251/462	0.79 (0.49-1.28)	0.29	NA	Goodman et al., 2009
Isoflavones	Genistein	Urinary	MEC	Japanese-American	Post-	112/216	0.62 (0.29-1.32)	0.08	NA	Goodman et al., 2009
Isoflavones	Genistein	Urinary	MEC	American (white)	Post-	51/96	0.98 (0.35-2.73)	0.79	NA	Goodman et al., 2009
Isoflavones	Genistein	Urinary	Prospective	Dutch	Post-	88/268	0.83 (0.46-1.51)	0.6	No effect modification by sample collection time before diagnosis	den Tonkelaar et al., 2001
Isoflavones	Dihydrogenistein	Urinary	SBCS	Chinese		250/250	0.57 (0.36-0.90)	0.01*	NA	Dai et al., 2002
Isoflavones	Daidzein	Plasma	EPIC Dutch	Dutch		388/388	0.83 (0.58-1.19)	0.33	NA	Verheus et al., 2007
Isoflavones	Daidzein	Plasma	JPHC	Japanese		144/288	0.71 (0.35-1.44)	0.54	NA	Iwasaki et al., 2008
Isoflavones	Daidzein	Plasma		Chinese		176/956	0.23 (0.12-0.48)	<0.0001*	NA	Lampe et al., 2007
Isoflavones	Daidzein	Plasma	JPHC	Japanese	Pre-	59/118	0.49 (0.15-1.57)	0.48	NA	Iwasaki et al., 2008
Isoflavones	Daidzein	Plasma	EPIC Dutch	Dutch	Pre- or peri-	87/87	0.80 (0.34-1.88)	0.44	NA	Verheus et al., 2007
Isoflavones	Daidzein	Plasma	EPIC Dutch	Dutch	Post-	296/296	0.88 (0.59-1.32)	0.59	NA	Verheus et al., 2007
Isoflavones	Daidzein	Plasma	JPHC	Japanese	Post-	80/160	1.16 (0.43-3.15)	0.95	NA	Iwasaki et al., 2008
Isoflavones	Daidzein	Serum	EPIC-Norfolk	English		97/187	1.220 (1.005-1.481)	0.044*	NA	Grace et al., 2004
Isoflavones	Daidzein	Serum	EPIC-Norfolk	English		219/891	1.04 (0.98-1.10)	0.225	No effect modification by ER+ status	Ward et al., 2008
Isoflavones	Daidzein	Urinary		Australian		144/144	0.47 (0.17-1.33)	0.241	NA	Ingram et al., 1997
Isoflavones	Daidzein	Urinary	EPIC-Norfolk	English		114/219	1.123 (0.963-1.309)	0.138	NA	Grace et al., 2004
Isoflavones	Daidzein	Urinary	EPIC-Norfolk	English		198/797	1.05 (0.99-1.10)	0.096	No effect modification by ER+ status	Ward et al., 2008
Isoflavones	Daidzein	Urinary	SBCS	Chinese		60/60	0.54 (0.22-1.32)	0.12	NA	Zheng et al., 1999
Isoflavones	Daidzein	Urinary	SBCS	Chinese		250/250	0.54 (0.34-0.85)	<0.01*	NA	Dai et al., 2002

Table 3. Continued

Flavonoid subclass	Certain compound	Bio-marker	Study[a]	Population	Menopausal status	Cases/ controls	Multivariate-adjusted OR[b]	P for trend[c]	Comments[d]	Reference
Isoflavones	Daidzein	Urinary	MEC	American (multiethnic)	Post-	251/462	0.76 (0.47-1.21)	0.07	NA	Goodman et al., 2009
Isoflavones	Daidzein	Urinary	MEC	Japanese-American	Post-	112/216	0.41 (0.19-0.89)	0.005*	NA	Goodman et al., 2009
Isoflavones	Daidzein	Urinary	MEC	American (white)	Post-	51/96	1.22 (0.46-3.22)	0.63	NA	Goodman et al., 2009
Isoflavones	Dihydrodaidzein	Urinary	SBCS	Chinese		250/250	0.73 (0.47-1.14)	0.08	NA	Dai et al., 2002
Isoflavones	Glycitein	Plasma	EPIC Dutch	Dutch		388/388	0.83 (0.59-1.18)	0.32	NA	Verheus et al., 2007
Isoflavones	Glycitein	Plasma	EPIC Dutch	Dutch	Pre- or peri-	87/87	0.92 (0.42-2.03)	0.85	NA	Verheus et al., 2007
Isoflavones	Glycitein	Plasma	EPIC Dutch	Dutch	Post-	296/296	0.81 (0.53-1.04)	0.34	NA	Verheus et al., 2007
Isoflavones	Glycitein	Serum	EPIC-Norfolk	English		97/187	1.226 (0.946-1.588)	0.123	NA	Grace et al., 2004
Isoflavones	Glycitein	Serum	EPIC-Norfolk	English		219/891	1.03 (0.97-1.10)	0.345	No effect modification by ER+ status	Ward et al., 2008
Isoflavones	Glycitein	Urinary	EPIC-Norfolk	English		114/219	1.076 (0.869-1.333)	0.499	NA	Grace et al., 2004
Isoflavones	Glycitein	Urinary	EPIC-Norfolk	English		198/797	1.03 (0.98-1.07)	0.248	No effect modification by ER+ status	Ward et al., 2008
Isoflavones	Glycitein	Urinary	SBCS	Chinese		60/60	0.41 (0.15-1.11)	0.06	NA	Zheng et al., 1999
Isoflavones	Glycitein	Urinary	SBCS	Chinese		250/250	0.42 (0.25-0.70)	<0.01*	NA	Dai et al., 2002
Isoflavones	O-Desmethylangolensin	Plasma	EPIC Dutch	Dutch		388/388	0.83 (0.59-1.18)	0.39	NA	Verheus et al., 2007
Isoflavones	O-Desmethylangolensin	Plasma	EPIC Dutch	Dutch	Pre- or peri-	87/87	0.66 (0.26-1.65)	0.32	NA	Verheus et al., 2007
Isoflavones	O-Desmethylangolensin	Plasma	EPIC Dutch	Dutch	Post-	296/296	0.82 (0.55-1.23)	0.64	NA	Verheus et al., 2007
Isoflavones	O-Desmethylangolensin	Serum	EPIC-Norfolk	English		97/187	1.140 (0.933-1.393)	0.199	NA	Grace et al., 2004
Isoflavones	O-Desmethylangolensin	Serum	EPIC-Norfolk	English		219/891	1.03 (0.97-1.09)	0.39	No effect modification by ER+ status	Ward et al., 2008
Isoflavones	O-Desmethylangolensin	Urinary	EPIC-Norfolk	English		114/219	1.148 (0.930-1.417)	0.198	NA	Grace et al., 2004
Isoflavones	O-Desmethylangolensin	Urinary	EPIC-Norfolk	English		198/797	1.02 (0.98-1.06)	0.25	No effect modification by ER+ status	Ward et al., 2008
Isoflavones	O-Desmethylangolensin	Urinary	SBCS	Chinese		250/250	0.72 (0.45-1.16)	0.15	NA	Dai et al., 2002
Isoflavones	Equol	Plasma	EPIC Dutch	Dutch		388/388	0.87 (0.63-1.21)		NA	Verheus et al., 2007
Isoflavones	Equol	Plasma	EPIC Dutch	Dutch	Pre- or peri-	87/87	0.81 (0.39-1.69)		NA	Verheus et al., 2007
Isoflavones	Equol	Plasma	EPIC Dutch	Dutch	Post-	296/296	0.91 (0.63-1.33)		NA	Verheus et al., 2007
Isoflavones	Equol	Serum	EPIC-Norfolk	English		97/187	1.455 (1.051-2.017)	0.024*	NA	Grace et al., 2004
Isoflavones	Equol	Serum	EPIC-Norfolk	English		219/891	1.04 (0.98-1.10)	0.167	No effect modification by ER+ status	Ward et al., 2008
Isoflavones	Equol	Urinary		Australian		144/144	0.27 (0.10-0.69)	0.009*	NA	Ingram et al., 1997
Isoflavones	Equol	Urinary	EPIC-Norfolk	English		114/219	1.344 (1.063-1.699)	0.013*	NA	Grace et al., 2004
Isoflavones	Equol	Urinary	EPIC-Norfolk	English		198/797	1.03 (0.99-1.06)	0.131	A significant association for ER+ tumors (OR 1.07, 95% CI 1.01-1.12; P for trend 0.013)	Ward et al., 2008
Isoflavones	Equol	Urinary	MEC	American (multiethnic)	Post-	251/462	0.99 (0.62-1.56)	0.8	NA	Goodman et al., 2009
Isoflavones	Equol	Urinary	MEC	Japanese-American	Post-	112/216	1.32 (0.70-2.49)	0.06	NA	Goodman et al., 2009
Isoflavones	Equol	Urinary	MEC	American (white)	Post-	51/96	0.27 (0.08-0.95)	0.07	NA	Goodman et al., 2009

[a], EPIC; The European Prospective Investigation into Cancer and Nutrition; JPHC, The Japan Public Health Center-based prospective study; MEC, The Multiethnic Cohort Study; SBCS, The Shanghai Breast Cancer Study; SWHS, The Shanghai Women`s Health Study; [b], OR; odds ratio; [c], Statistically significant effects (p for trend <0.05) are marked by asterisk; [d], BMI; body mass index; E1-S, estrone sulfate; E2, estradiol; ER, estrogen receptor; NA, not applicable; SHBG, sex hormone-binding globulin; WHR, waist-to-hip ratio

habitual preference and these intake levels are relatively stable over time for most individuals, it is possible that breast cancer cases have altered their eating habits after cancer diagnosis or modified their diets just before sample collection (Zheng et al., 1999; den Tonkelaar et al., 2001; Lampe et al., 2007; Luo et al., 2010; Chen et al., 2014). In several epidemiological studies, only a single spot urine or one plasma sample were measured and these parameters may not reflect and represent the usual long-term human exposure levels (Trock et al., 2006; Luo et al., 2010). The possibilities of metabolic changes in biotransformation of flavonoids developed in consequence of breast carcinogenesis can also be not excluded (den Tonkelaar et al., 2001; Peterson et al., 2003; Iwasaki et al., 2008).

An additional factor possibly affecting the association between dietary intake of flavonoids (isoflavones) and breast cancer risk may come from the timing of consumption of isoflavone-rich food items (Travis et al., 2008; Morimoto et al., 2014). The protective effect of soy foods intake reported in several Asian studies can be related to the early life or continuous long-term exposure to isoflavones (Keinan-Boker et al., 2004; Travis et al., 2008; Dong and Qin, 2011; Kang et al., 2012; Wada et al., 2013; Xie et al., 2013; Zamora-Ros et al., 2013). Consumption of isoflavones in higher amounts since childhood or adolescence (prepubertally) may affect the maturation of mammary gland and therefore influence also the risk of breast cancer incidence in later life (Thanos et al., 2006; Lampe et al., 2007; Ward et al., 2008; Nagata, 2010; Xie et al., 2013). Because of majority of Western women have not experienced sufficient early-life exposure to soy foods the beneficial health effects could not be expressed (Morimoto et al., 2014). However, it is difficult to decide whether recent dietary intake of flavonoids can reflect the intake patterns during the time periods which are most relevant to tumor initiation and development, making it possible that these age intervals were missed in several epidemiological studies (Keinan-Boker et al., 2004; Adebamowo et al., 2005; Fink et al., 2007; Ward et al., 2008). In future, it would be interesting to study the effects of in utero exposure to isoflavones through maternal soy consumption on breast cancer risk in older age.

The power to draw consequences in epidemiological studies can be limited due to the small numbers of participants, particularly in the stratified analyses with restricted subgroups (Adebamowo et al., 2005; Cho et al., 2010; Zhu et al., 2011). Some variations in the findings of risk association can be attributed to the differences in study design, i.e. case-control versus prospective cohort studies. Interpretation of results from case-control studies are typically more complicated as reported parameters among cases might have influenced by disease, both directly inducing metabolic alterations or indirectly through dietary changes or stress (dos Santos Silva et al., 2004). Therefore, any case-control studies suffer several potential limitations, including recall bias as cancer patients may describe their dietary habits differently than controls (Horn-Ross et al., 2002; Thanos et al., 2006; Cotterchio et al., 2008; Iwasaki et al., 2009a; Cho et al., 2010; Dong and Qin, 2011; Zamora-Ros et al., 2013). This study design is susceptible also to selection bias that can still be avoided by proper choosing of cases and controls from the same cohort (Trock et al., 2006; Cotterchio et al., 2008; Iwasaki et al., 2008; Dong and Qin, 2011). Selection of controls from non-cancer inpatients or outpatients in hospital can involve some measurement errors because of their different dietary habits compared to the general population (Hirose et al., 2005; Zhang et al., 2010; Li et al., 2013). In addition, the possibility still remains that control subjects who voluntarily agree to participate might be more conscious of healthy eating and lifestyle than the general population of females not suffering from breast cancer (Ingram et al., 1997; den Tonkelaar et al., 2001; Trock et al., 2006). Prospective cohort study design has several preferences being free from differential bias in reported dietary data, since information of consumption is collected before breast cancer diagnosis (Yamamoto et al., 2003; Iwasaki et al., 2010; Wada et al., 2013; Morimoto et al., 2014). Also, longer-term follow-up periods can be applied in these large-scale studies. However, estimating the flavonoids intake only once in baseline of study can entail measurement errors in those participants who alter their dietary patterns during follow-up years. Moreover, patients could have modified their dietary habits during early prediagnostic period due to preclinical signs of disease (Wada et al., 2013; Zamora-Ros et al., 2013).

While many probable confounders were considered in the association studies between intake of flavonoids and breast cancer risk, confounding by other known and unknown factors cannot be fully excluded (Peterson et al., 2003; Yamamoto et al., 2003; dos Santos Silva et al., 2004; Grace et al., 2004; Cotterchio et al., 2008; Iwasaki et al., 2008; Wada et al., 2013; Wang et al., 2014). It is possible that abundant consumption of flavonoids-containing food items (such as fruits and vegetables) may be associated with an overall healthy diet and lifestyle or ingestion of other anticancer substances, or be a marker for other characteristics related to susceptibility toward mammary carcinogenesis (Thanos et al., 2006; Fink et al., 2007; Lee et al., 2009; Dong and Qin, 2011; Xie et al., 2013). Regarding to the effects of isoflavones being often evaluated by the consumption of soy foods, other bioactive constituents in soy may also exert beneficial action on breast cancer risk (Bouker and Hilakivi-Clarke, 2000; Wu et al., 2002; Cho et al., 2010). In addition, in several epidemiological studies the information about expression of estrogen and progesterone receptors in tumor tissue as well as the menopausal or equol-producer status of participants are unknown, although these factors can potentially modify the relationships between flavonoids and breast cancer (Travis et al., 2008; Dong and Qin, 2011; Hui et al., 2013; Wada et al., 2013; Chen et al., 2014). It has been hypothesized that isoflavones act as estrogen receptor agonists in low-endogenous-estrogen conditions typical for postmenopausal women and as antagonists in high-endogenous-estrogen environment observed in premenopausal women (Fink et al., 2007; Cho et al., 2010; Nagata, 2010; Dong and Qin, 2011; Wada et al., 2013). Although, findings of epidemiological studies are inconclusive, greater impact among postmenopausal women can suggest that emerging of effect through habitual dietary consumption of isoflavones can take

a long time (Fink et al., 2007; Cho et al., 2010; Hui et al., 2013; Wada et al., 2013). Also, premenopausal and postmenopausal breast tumors may have separate disease etiologies and the biological role of flavonoids in breast carcinogenesis may be mediated by mechanisms involving the synthesis of sex hormones in ovaries or alteration of other characteristics of menstrual cycle (Travis et al., 2008; Zhang et al., 2010; Zhu et al., 2011; Hui et al., 2013; Zamora-Ros et al., 2013). The dependence of isoflavones activity on hormonal milieu is reflected also by stratification of association findings according to obesity characteristics, i.e. body mass index (BMI) and waist-to-hip ratio (WHR) (Iwasaki et al., 2008). Besides hormonal effects, flavonoids exert also antioxidant, antiproliferative, antiangiogenic and anti-inflammatory activities, all of which, singly or combined, can contribute to the protective action of these phytochemicals against breast carcinogenesis (Iwasaki et al., 2009a; Hui et al., 2013; Wada et al., 2013).

Last but not least, inconsistencies in the epidemiological findings about associations between intake of flavonoids and breast cancer risk may be explained also by diet-gene interactions (Hedelin et al., 2008; Zhang et al., 2009; Cho et al., 2010). Although this knowledge is still rather scarce today, the protective effect of isoflavones against mammary tumorigenesis was limited only to those postmenopausal Japanese, Japanese Brazilian and non-Japanese Brazilian women who carried the GG genotype of the rs4986938 single nucleotide polymorphism in the estrogen receptor beta (ESR2) gene (Iwasaki et al., 2009b). Also, the genetic variations in DNA repair genes may modify the protective action of isoflavones on breast cancer (Khankari et al., 2014).

Conclusions and further perspectives

Despite numerous experimental data demonstrating anticancer action of flavonoids *in vitro* conditions and animal experiments (Sak, 2014), epidemiological findings about the association between intake of these plant-based polyphenols and breast cancer risk have produced inconsistent results. The heterogeneity between findings of different studies can be caused by various reasons, including the study design (retrospective works are sensitive to recall bias, differently from prospective studies), dose and timing of exposure to flavonoids, menopausal status of women, and subtype of breast tumor.

The current review demonstrates that probably the most apparent relationship prevails for consumption of isoflavones, whereas beneficial effects seem to be expressed only at high intake levels typical to Asian women providing some explanations also to the reduced incidence rate of mammary tumors in Asian populations compared to Western countries where the intake of soy products is remarkably low. Moreover, protective activities of isoflavones might appear only in females consuming soy foods since their early age as childhood and adolescence can be crucial periods of exposure. Therefore, consumption of dietary phytochemicals could play a significant protective role against breast carcinogenesis and if confirmed, these findings increase the attractiveness to use isoflavones-containing food items as potential chemopreventive agents and suggest also the importance to initiate the cancer prevention at early age. As diet is a potentially modifiable factor in our life, the conclusions of this review may have significant implications for public health and can be used also by healthcare professionals in consulting the patients on prevention of breast tumor. However, it is self-evident that before this, more large-scale studies are needed to further investigate the effects of dose and exposure timing to flavonoids, form and source of these phytochemicals, their potential mechanisms in carcinogenesis, impact of food matrix, interactions between diet and genes, ethnicity of participants, their good and bad health habits like smoking and alcohol consumption, role of specific tumor characteristics and level of endogenous hormones among several other more or less important factors. In the current stage, recommendations for consumption of high-dose isoflavones from food items or supplements to reduce the individual susceptibility toward breast carcinogenesis are still premature and can also be not completely without the risks.

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