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

REVIEW

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

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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,
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., 2014; Pantavos et al., 2015).
| Flavonoid subclass | Study          | Population | Controls | Cases | Reference |
|-------------------|----------------|------------|----------|-------|-----------|
| Flavanols         | Mexican        | 2569/2588  | 141/141  |       | Fink et al., 2007 |
|                   | Greek          | 820/1548   | 141/141  |       | Fink et al., 2007 |
|                   | American       | 2569/2588  | 141/141  |       | Fink et al., 2007 |
|                   | Mexican        | 2569/2588  | 141/141  |       | Fink et al., 2007 |
|                   | Greek          | 820/1548   | 141/141  |       | Fink et al., 2007 |
|                   | American       | 2569/2588  | 141/141  |       | Fink et al., 2007 |
|                   | Mexican        | 2569/2588  | 141/141  |       | Fink et al., 2007 |
|                   | Greek          | 820/1548   | 141/141  |       | Fink et al., 2007 |
|                   | American       | 2569/2588  | 141/141  |       | Fink et al., 2007 |
|                   | Mexican        | 2569/2588  | 141/141  |       | Fink et al., 2007 |
|                   | Greek          | 820/1548   | 141/141  |       | Fink et al., 2007 |
|                   | American       | 2569/2588  | 141/141  |       | Fink et al., 2007 |
|                   | Mexican        | 2569/2588  | 141/141  |       | Fink et al., 2007 |
|                   | Greek          | 820/1548   | 141/141  |       | Fink et al., 2007 |
|                   | American       | 2569/2588  | 141/141  |       | Fink et al., 2007 |
|                   | Mexican        | 2569/2588  | 141/141  |       | Fink et al., 2007 |
|                   | Greek          | 820/1548   | 141/141  |       | Fink et al., 2007 |
|                   | American       | 2569/2588  | 141/141  |       | Fink et al., 2007 |
|                   | Mexican        | 2569/2588  | 141/141  |       | Fink et al., 2007 |
|                   | Greek          | 820/1548   | 141/141  |       | Fink et al., 2007 |
|                   | American       | 2569/2588  | 141/141  |       | Fink et al., 2007 |

Table 1. Epidemiological Case-Control Studies on Dietary Intake of Flavonoids and Breast Cancer Risk
| Reference                        | Population          | PB          | Controls | Menopausal status | Cases/controls | Intake comparison (low vs high, mg/day) | Multivariate-adjusted OR/RR/HRd | P for trendे | Commentsf |
|---------------------------------|---------------------|-------------|----------|-------------------|----------------|----------------------------------------|--------------------------------|-------------|-----------|
| Fink et al., 2007               | American (multiethnic, non-Asian) | LIBCSP      | 1434/1440 | <1.048 vs ≥2.775 (Q4) | 0-0.31 vs ≥7.63 (Q5) | 0.95 (0.74-1.22) | 0.31                   | NA          |           |
| Horn-Ross et al., 2001          | Chinese             | 1272/1610   | <1.048 vs ≥2.775 (Q4) | 1.0 vs 1.5 (T1) | 1.2 (0.75-2.0) | 0.31                   | NA          |           |
| Wu et al., 2002                 | Asian-American (multiethnic) | PB          | 501/594   | ≤1.79 vs >12.68 /1000 kcal (Q4) | 0.61 (0.39-0.97) | 0.04* | NA          |           |
| Cotterchio et al., 2008         | Canadian            | OWDHS       | 3000/3370 | 0-0.082 vs 1.237-158.983 (Q5) | 1.06 (0.87-1.30) | 0.31                   | NA          |           |
| Thanos et al., 2006             | Greek               | 820/1548    | 0.01 vs 0.8 (Q5) | 0.76 vs 0.9 (Q6) | 1.07 (0.97-1.18) | 0.17                   | NA          |           |
| Fink et al., 2007               | Chinese             | 2569/2588   | <8.5 vs ≥23.7 (Q4) | 1.0 vs 1.5 (T1) | 1.05 (0.86-1.29) | 0.78                   | NA          |           |
| Cho et al., 2010                | Japanese            | HB          | 358/360   | <8.5 vs ≥23.7 (Q4) | 0.81 (0.48-1.38) | 0.823                  | NA          |           |
| Iwasaki et al., 2009a           | Japanese Brazilian  | HB          | 81/81     | 4.7 vs 42.8 (T3) | 0.25 (0.09-0.68) | <0.01*                  | NA          |           |
| Iwasaki et al., 2009a           | Brazilian (non-Japanese) | HB          | 379/379   | 0 vs 15.0 (non- vs consumers) | 0.56 (0.35-0.90) | * | NA          |           |
| Li et al., 2013                 | Chinese             | PB          | 295/295   | <12.49 vs >35.12 (Q4) | 0.45 (0.27-0.75) | <0.01*                  | NA          |           |
| Li et al., 2013                 | Chinese             | HB          | 438/438   | <3.26 vs >16.89 (Q4) | 0.54 (0.34-0.84) | 0.001*                  | NA          |           |
| Zhang et al., 2009              | Chinese             | HB          | 183/192   | <7.56 vs >28.83 (T4) | 0.42 (0.22-0.80) | 0.031*                  | NA          |           |
| Zhu et al., 2011                | Chinese             | HB          | 183/192   | <7.78 vs >25.40 (Q4) | 0.42 (0.22-0.80) | 0.031*                  | NA          |           |
| Flavonoid subclass | Certain compound | Study | Population | Controls | Menopausal status | Cases/controls | Intake comparison (low vs high, mg/day) | Multivariate-adjusted OR/RR/HR | P for trend | Comments |
|-------------------|------------------|-------|------------|----------|------------------|---------------|--------------------------------|-----------------|------------|----------|
| Isoflavones       |                   |       | OWDHS      | Canadian | Pre-930/1211     | 0-0.082 vs 1.237 | 158.983 (Q5) | 0.96 (0.69-1.33) | 0.96 | No effect modification by BMI strata (≤25, >25) |
|                   |                   |       | German PB  | Pre-278/666 |                             | 0.85 (0.54-1.33) | 0.229 | NA |       |
|                   |                   |       | Korean PB  | Pre-358/360 | <8.5 vs ≥23.7 (Q4) | 1.36 (0.64-2.91) | 0.209 | No effect modification by ER/PR status |       |
|                   |                   |       | Japanese HB | Pre-79/414 | 7.61 vs 18.47/1000 kcal (T3) | 0.44 (0.22-0.89) | 0.02* | NA |       |
|                   |                   |       | 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 |       |
|                   |                   |       | Japanese Brazilian HB | Pre-25/24 | 8.0 vs 35.0 (two medians) | 0.17 (0.03-0.84) | * | NA |       |
|                   |                   |       | Brazilian (non-Japanese) HB | Pre-161/145 | 0 vs 15.0 (non-consumers) | 0.54 (0.26-1.13) | NA |       |
|                   |                   |       | Chinese HB | Pre-306/295 | <7.78 vs >25.40 (Q4) | 0.46 (0.26-0.82) | <0.001* | NA |       |
|                   |                   |       | Chinese HB | Pre-183/192 | <7.56 vs >28.83 (Q4) | 0.66 (0.31-1.07) | NA |       |
|                   |                   |       | American PB (multiethnic, non-Asian) | Pre-826/1077 | <1.048 vs ≥2.775 (Q4) | 0.96 (0.71-1.3) | NA |       |
|                   |                   |       | OWDHS (multinational, non-Asian) | Post-977/953 | 0-0.31 vs ≥7.63 (Q5) | 1.02 (0.76-1.38) | 0.72 |       |
|                   |                   |       | French (multiethnic, non-Asian) | Post-1100/1101 | 0.22 vs 1.39 (T3) | 1.09 (0.83-1.41) | No effect modification by BMI strata (≤25, >25) |       |
|                   |                   |       | Chinese | Post-132/143 | (Q4) | 0.66 (0.30-1.44) | 0.281 |       |
|                   |                   |       | Korean | Post-358/360 | <8.5 vs ≥23.7 (Q4) | 0.66 (0.30-1.44) | 0.281 |       |
|                   |                   |       | Japanese | Post-212/253 | 22.1 vs 69.1 (T3) | 0.62 (0.38-1.01) | NA |       |
|                   |                   |       | Japanese Brazilian | Post-56/57 | 8.0 vs 35.0 (two medians) | 0.84 (0.37-1.92) | NA |       |
|                   |                   |       | Brazilian (non-Japanese) | Post-218/234 | 0 vs 15.0 (non-consumers) | 0.58 (0.33-1.03) | NA |       |
|                   |                   |       | Chinese | Post-183/192 | <7.56 vs >28.83 (Q4) | 0.57 (0.29-0.83) | * |       |
|                   |                   |       | Chinese | Post-183/192 | <7.56 vs >28.83 (Q4) | 0.57 (0.29-0.83) | * |       |

Table 1. Continued

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| Flavonoid subclass | Certain compound | Studya Population | Controlsb | Meno-pausal status | Cases/ controls | Intake comparison | Multivariate- adjusted OR/RR/HRe | P for trend | 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 |
|                   |                  | EPIC-Norfolk English | PB | 244/938 | 1.04 (0.90-1.19) | 0.63 | NA | Ward et al., 2010 |
|                   |                  | South Asian in England | PB | 240/477 | <0.078 vs ≥0.232 (Q4) | 0.62 (0.36-1.06) | 0.10 | dos Santos Silva et al., 2004 |
|                   |                  | JPHC Japanese | PB | 144/288 | (Q4) | 0.58 (0.29-1.18) | 0.21 | Iwasaki et al., 2008 |
|                   |                  | Chinese | HB | 295/295 | <8.46 vs >25.44 (Q4) | 0.34 (0.19-0.60) | <0.01* | Li et al., 2013 |
|                   |                  | Chinese | PB | 295/295 | <8.46 vs >25.44 (Q4) | 0.28 (0.15-0.52) | <0.01* | Li et al., 2013 |
|                   |                  | Chinese | HB | /1009 | <4.27 vs >14.18 (Q4) | * | No effect modification by ER/PR status | Zhang et al., 2009 |
|                   |                  | JPHC Japanese | PB | Pre- | 59/118 | (Q4) | 0.62 (0.21-1.84) | 0.43 | Iwasaki et al., 2008 |
|                   |                  | Chinese | HB | Pre- | /671 | <4.27 vs >14.18 (Q4) | * | No effect modification by ER/PR status | Zhang et al., 2009 |
|                   |                  | Chinese | Post- | 80/160 | (Q4) | 0.52 (0.19-1.42) | 0.31 | Iwasaki et al., 2008 |
|                   |                  | Chinese | HB | Post- | /338 | <4.27 vs >14.18 (Q4) | * | No effect modification by ER/PR status | Zhang et al., 2009 |
|                   | 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 |
|                   |                  | EPIC-Norfolk English | PB | 244/938 | 1.03 (0.89-1.18) | 0.70 | NA | Ward et al., 2010 |
|                   |                  | German | PB | Pre- | 278/666 | (Q4) | 0.62 (0.40-0.95) | 0.065 | Linseisen et al., 2004 |
|                   |                  | South Asian in England | PB | 240/477 | <0.078 vs ≥.0232 (Q4) | 0.57 (0.33-0.99) | 0.09 | dos Santos Silva et al., 2004 |
|                   |                  | JPHC Japanese | PB | Pre- | 59/118 | (Q4) | 0.67 (0.22-2.03) | 0.53 | Iwasaki et al., 2008 |
|                   |                  | Chinese | HB | Pre- | /671 | <2.98 vs >9.76 (Q4) | * | No effect modification by ER/PR status | Zhang et al., 2009 |
|                   |                  | JPHC Japanese | PB | Post- | 80/160 | (Q4) | 0.64 (0.23-1.72) | 0.43 | Iwasaki et al., 2008 |
|                   |                  | Chinese | HB | Post- | /338 | <2.98 vs >9.76 (Q4) | * | No effect modification by ER/PR status | Zhang et al., 2009 |
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| Flavonoid subclass | Certain compound | Study | Population | Controls | Menopausal status | Cases/controls | Intake comparison (low vs high, mg/day) | Multivariate-adjusted OR/RR/HR | P for trend | Comments |
|--------------------|------------------|-------|------------|----------|------------------|---------------|------------------------------------------|-------------------------------|-----------|----------|
| Isoflavones        | Biochanin A      | American (multiethnic, non-Asian) PB | 1272/1610 | <0.022 vs ≥0.083 (Q4) | 0.85 vs 1.0 (Q5) | 0.96 vs 1.0 (Q5) | 1.2 vs 0.96 (Q5) | 1.2 vs 0.96 (Q5) | 0.048 | NA       |
|                    |                  | EPIC-Norfolk English PB | 244/938  | 1.10 (0.90-1.34) | 0.94 (0.81-1.09) | 0.94 (0.81-1.09) | 1.14 vs 0.96 (Q5) | 1.14 vs 0.96 (Q5) | 0.36  | NA       |
|                    |                  | German PB Pre | 278/666  | 0.85 (0.53-1.38) | 1.14 (0.96-1.32) | 1.14 (0.96-1.32) | 0.85 (0.53-1.38) | 0.85 (0.53-1.38) | 0.747 | NA       |
| Isoflavones        | Formononetin     | American (multiethnic, non-Asian) PB | 1272/1610 | <0.009 vs ≥0.040 (Q4) | 0.96 vs 1.0 (Q5) | 0.96 vs 1.0 (Q5) | 1.2 vs 0.96 (Q5) | 1.2 vs 0.96 (Q5) | 0.009 | NA       |
|                    |                  | EPIC-Norfolk English PB | 244/938  | 0.94 (0.81-1.09) | 0.94 (0.81-1.09) | 0.94 (0.81-1.09) | 0.94 (0.81-1.09) | 0.94 (0.81-1.09) | 0.44  | NA       |
|                    |                  | German PB Pre | 278/666  | 1.14 (0.72-1.82) | 1.14 (0.72-1.82) | 1.14 (0.72-1.82) | 1.14 (0.72-1.82) | 1.14 (0.72-1.82) | 0.395 | NA       |
| Isoflavones        | Glycitein        | American (multiethnic, non-Asian) HB | 295/295  | <0.38 vs >1.46 (Q4) | 0.66 (0.40-1.08) | 0.66 (0.40-1.08) | 0.55 (0.33-0.92) | 0.55 (0.33-0.92) | 0.02* | NA       |
|                    |                  | Chinese HB Pre | 295/295  | <1.19 vs >6.32 (Q4) | 0.55 (0.33-0.92) | 0.55 (0.33-0.92) | 0.55 (0.33-0.92) | 0.55 (0.33-0.92) | 0.02* | NA       |
|                    |                  | Chinese HB Post | 295/295  | <1.19 vs >6.32 (Q4) | 0.55 (0.33-0.92) | 0.55 (0.33-0.92) | 0.55 (0.33-0.92) | 0.55 (0.33-0.92) | 0.02* | NA       |
| Anthocyanidins     | LIBCSP            | American PB Pre | 457/487  | 0-0.04 vs ≥4.20 (Q5) | 1.08 (0.71-1.63) | 1.08 (0.71-1.63) | 1.08 (0.71-1.63) | 1.08 (0.71-1.63) | 0.81  | NA       |
|                    |                  | American PB Post | 977/953  | 0-0.04 vs ≥4.20 (Q5) | 0.85 (0.64-1.14) | 0.85 (0.64-1.14) | 0.85 (0.64-1.14) | 0.85 (0.64-1.14) | 0.23  | No effect modification by ER/PR status |
|                    |                  | Greek Case-control | 820/1548 | 5.1 vs 81.4 (Q5) | 0.94 (0.81-1.09) | 0.94 (0.81-1.09) | 0.94 (0.81-1.09) | 0.94 (0.81-1.09) | 0.39  | NA       |
|                    |                  | Italian HB | 2569/2588 | 1.09 (0.87-1.36) | 0.94 (0.81-1.09) | 0.94 (0.81-1.09) | 0.94 (0.81-1.09) | 0.94 (0.81-1.09) | 0.38  | NA       |
|                    |                  | American LIBCSP | Pre | 457/487  | 0-0.04 vs ≥4.20 (Q5) | 1.08 (0.71-1.63) | 1.08 (0.71-1.63) | 1.08 (0.71-1.63) | 1.08 (0.71-1.63) | 0.81  | NA       |
|                    |                  | American LIBCSP | Post | 977/953  | 0-0.04 vs ≥4.20 (Q5) | 0.85 (0.64-1.14) | 0.85 (0.64-1.14) | 0.85 (0.64-1.14) | 0.85 (0.64-1.14) | 0.23  | No effect modification by ER/PR status |

Table 1. Continued
remarkable reduction in the risk of both fibrocystic breast with high urinary levels of equol, a metabolite produced reduction in breast tumor incidence in Australian women of daidzein and Ingram (1997) indicated almost four-fold Japanese American women with higher urinary excretion a decreased risk of breast cancer in postmenopausal of a small sample size. Goodman (2009) described did not reach statistical significance probably because (genistein, daidzein, glycitein), although these results 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).

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 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 equl, 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.
| Authors and Year       | Country          | Cases/ Cohort | Median | Reference | Comments |
|-----------------------|------------------|---------------|--------|-----------|----------|
| Adebamowo et al., 2016| American         | 316           | 59/201 |           |          |
| Goldbohm et al., 1998 | European countries | 0.591         | 1102/954 |           |          |
| Wang et al., 2014     | American         | 0.656         | 87/9959 |           |          |
| Zamora-Ros et al., 2013| European countries | 0.591         | 11576/334850 |           |          |
| Pantavos et al., 2015 | European countries | 1.53          | 23.5 vs 30.9 (Q4) |           |          |
| Zhu et al., 2012      | European countries | 0.74          | 102.3 vs 90.6 (Q5) |           |          |
| Wang et al., 2014     | American         | 0.66          | 2116/56630 |           |          |
| Zamora-Ros et al., 2013| European countries | 0.591         | 11576/334850 |           |          |
| Pantavos et al., 2015 | European countries | 1.53          | 23.5 vs 30.9 (Q4) |           |          |
| Zhu et al., 2012      | European countries | 0.74          | 102.3 vs 90.6 (Q5) |           |          |
| Wang et al., 2014     | American         | 0.66          | 2116/56630 |           |          |
### Table 2. Continued

| Reference | Flavonoid subclass | Compound | Study | Median follow-up (years) | Menopausal status in baseline | Cases/ cohort | Intake comparison (low vs high, mg/day) | Multivariate-adjusted OR/RR/HR | P for trend | Comment |
|-----------|--------------------|----------|-------|--------------------------|-------------------------------|---------------|------------------------------------------|-------------------------------|-------------|---------|
| Goldbohm et al., 1998 | Flavonols | Kaempferol | NLCS | 4.3 | 605/3123 | 2.6 vs 12.9 (Q5) | 1.02 (0.72-1.45) | 0.286 | NA | |
| Knekt et al., 2002 | Flavonols | Kaempferol | FMC | 30 | 125/4647 | 0.2 vs 0.9 (Q4) | 0.87 (0.53-1.41) | 0.7 | NA | |
| Adebamowo et al., 2005 | Flavonols | Kaempferol | NHS II | 8 | Pre | 710/90638 | 0.8 vs 12.9 (Q5) | 1.01 (0.80-1.27) | 0.91 | NA | |
| Knekt et al., 2002 | Flavonols | Myricetin | FMC | 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 | 8 | Pre | 710/90638 | 0.09 vs 2.62 (Q5) | 0.99 (0.78-1.26) | 0.35 | NA | |
| Goldbohm et al., 1998 | Flavonols | Myricetin | NLCS | 4.3 | 605/3123 | 8.9 vs 30.8 (Q5) | 1.00 (0.70-1.41) | 0.957 | NA | |
| Knekt et al., 2002 | Flavonols | Myricetin | FMC | 30 | 125/4647 | 1.8 vs 4.7 (Q4) | 0.62 (0.37-1.03) | 0.25 | NA | |
| Adebamowo et al., 2005 | Flavonols | Myricetin | NHS II | 8 | Pre | 710/90638 | 5.3 vs 30.1 (Q5) | 1.05 (0.83-1.33) | 0.81 | NA | |
| Zamora-Ros 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 | |
| Touvier 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 |
| Zamora-Ros et al., 2013 | Flavanones | EPIC | Women from ten European countries | 11.5 | Pre | 2827/334850 | <6.2 vs >33.0 (Q5) | 1.04 (0.95-1.15) | 0.401 | NA | |
| Wang et al., 2014 | 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 |
| Zamora-Ros et al., 2013 | 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 | |
| Knekt et al., 2002 | Flavanones | Hesperetin | FMC | 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 | 30 | 125/4647 | 0.9 vs 7.7 (Q4) | 1.14 (0.67-1.94) | 0.82 | NA | |
| Zamora-Ros et al., 2013 | 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 |
| Touvier 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 |
| Zamora-Ros 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 | |
| Wang et al., 2014 | 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 | |
| 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 | Flavanols | IWHS | American | 13 | Post | 1069/34651 | 3.6 vs 75.1 (Q5) | 1.04 (0.84-1.28) | 1 | NA | |
| Zamora-Ros et al., 2013 | 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 | Flavanols | IWHS | American | 13 | Post | 1069/34651 | 3.6 vs 75.1 (Q5) | 1.04 (0.84-1.28) | 1 | NA | |
### Table 2. Continued

| Flavonoid | Subclass | Certain | Compound | Study | Population | Median follow-up (years) | Menopausal status in baseline | Cases/ cohort | Intake comparison (low vs high, mg/day) | Multivariate-adjusted OR/RR/HR | P for trend | Comments |
|-----------|----------|---------|----------|-------|------------|--------------------------|--------------------------------|--------------|-----------------------------------------|---------------------------------|------------|----------|
| Isoflavones | ME | American, Hawaiian (multiethnic) | 13.7 | 4769/84450 | 1.7 vs 29.6 (Q4) | 0.96 (0.85-1.08) | >0.10 | 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 | 13 | 1014/45448 | 0.98 (0.83-1.17) | >0.98 | NA | 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 | 6.29 | 3629/35303 | <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 | 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 | 196/37643 | <10 vs >10 | 1.31 (0.95-1.81) | >0.11 | NA | Travis et al., 2008 |
| Isoflavones | E3N | French | 12 | 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 |
| Isoflavones | TS | Japanese | 15.5 | 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 | 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 | | | | | | | | |
| Isoflavones | CPS-II | American | 8.5 | 2196/56630 | ≤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 | 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 | 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 | 310/37643 | <10 vs >10 | 0.95 (0.66-1.38) | >0.8 | NA | Travis et al., 2008 |
| Isoflavones | TS | Japanese | 15.5 | 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, drinkers | Wada et al., 2013 |
### Table 2. Continued

| Flavonoid Subclass | Study | Population | Median Follow-up (Years) | Menopausal Status in Baseline | Cases/Cohort | Intake Comparison (Low vs High, mg/day) | Multivariate-Adjusted OR/RR/HR | P for Trend | Comments |
|--------------------|-------|------------|---------------------------|------------------------------|--------------|----------------------------------------|-------------------------------|-------------|----------|
| Isoflavones        | SWHS  | Chinese    | Post-289/73223            | 11.23 vs 54.97 (Q5)        | 1.09 (0.78-1.52) | 0.8 | NA | 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 |
|                    | SCHS  | Singapore Chinese | Post-439/35303 | 10.6 vs ≥10.6 /1000 kcal | 0.74 (0.61-0.90) | 0.003* | | |
| Isoflavones        | CTS   | American   | 2 711/111526             | (Q5) | 1.0 (0.7-1.3) | 0.9 | NA | |
|                    | WLH   | Swedish    | 13 1014/45448            | (Q4) | 1.01 (0.84-1.20) | 0.9 | NA | No effect modification by age strata (<50, ≥50 y) |
|                    | JPHC  | Japanese   | 10 179/21852             | 6.9±2.6 vs 25.3±2.2 (Q4) | 0.46 (0.25-0.84) | 0.043* | | |
|                    |          |            |                          | 89/21852                   | 0.66 (0.25-1.7) | 0.97 | NA | |
|                    | JPHC  | Japanese   | 10 87/21852              | (Q4) | 0.32 (0.14-0.71) | 0.006* | | |
| Isoflavones        | CTS   | American   | 2 711/111526             | (Q5) | 0.9 (0.7-1.2) | 0.6 | NA | |
|                    | WLH   | Swedish    | 13 1014/45448            | (Q4) | 1.07 (0.90-1.28) | | | Non-to-low alcohol users; increased risk in higher drinkers |
| Isoflavones        | CTS   | American   | 2 711/111526             | (Q5) | 1.0 (0.8-1.3) | 0.7 | NA | |
|                    | CTS   | American   | 2 711/111526             | (Q5) | 1.1 (0.8-1.4) | 0.4 | NA | |
| 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 |
|                    | 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 |
| Anthocyanins       | EPIC  | Women from ten European countries | 11.5 | 2827/334850 | <12.1 vs >43.6 (Q5) | 1.09 (0.93-1.28) | 0.323 | |
|                    | EPIC  | Women from ten European countries | 11.5 | 5872/334850 | <12.1 vs >43.6 (Q5) | 1.01 (0.90-1.13) | 0.829 | |
| Anthocyanidins     | CPS-II | American | 8.5 | 2116/56630 | ≤5.3 vs >16.1-97.9 (Q5) | 0.91 (0.80-1.05) | 0.52 | No effect modification by ER status |
|                    | EPIC  | Women from ten European countries | 11.5 | 5872/334850 | <12.1 vs >43.6 (Q5) | 1.01 (0.90-1.13) | 0.829 | |
|                |       |            | | | | | | |

**Legend:**
- **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

**Abbreviations:**
- OR, odds ratio; RR, relative risk; HR, hazard ratio
- Statistically significant effects (p for trend <0.05) are marked by asterisk
- ER, estrogen receptor; HRT, hormone replacement therapy; PR, progesterone receptor; NA, not applicable

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*Note: The table continues on the next page.*
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; Adedamowo 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 (Adedamowo 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 flavonoid-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; Adedamowo 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
| Study | Type | Country | Control | Cases | Odds Ratio | 95% CI | P Value |
|-------|------|---------|---------|------|------------|--------|---------|
| Luo et al., 2010 | Serum | Chinese | 250/250 | 353/701 | 1.11 | 0.43-2.84 | 0.92 |
| Luo et al., 2010 | Plasma | Chinese | 59/118 | 59/118 | 1.15 | 0.43-3.11 | 0.11 |
| Luo et al., 2010 | Plasma | Japanese | 59/118 | 59/118 | 1.78 | 0.66-4.79 | 0.344 |
| Luo et al., 2010 | Urinary | Japanese | 59/118 | 59/118 | 1.11 | 0.43-2.84 | 0.92 |
| Luo et al., 2010 | Urinary | Japanese | 59/118 | 59/118 | 1.15 | 0.43-3.11 | 0.11 |
| Luo et al., 2010 | Urinary | Chinese | 250/250 | 353/701 | 1.11 | 0.43-2.84 | 0.92 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.15 | 0.43-3.11 | 0.11 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.78 | 0.66-4.79 | 0.344 |
| Luo et al., 2010 | Urinary | Chinese | 250/250 | 353/701 | 1.11 | 0.43-2.84 | 0.92 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.15 | 0.43-3.11 | 0.11 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.78 | 0.66-4.79 | 0.344 |
| Luo et al., 2010 | Urinary | Chinese | 250/250 | 353/701 | 1.11 | 0.43-2.84 | 0.92 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.15 | 0.43-3.11 | 0.11 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.78 | 0.66-4.79 | 0.344 |
| Luo et al., 2010 | Urinary | Chinese | 250/250 | 353/701 | 1.11 | 0.43-2.84 | 0.92 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.15 | 0.43-3.11 | 0.11 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.78 | 0.66-4.79 | 0.344 |
| Luo et al., 2010 | Urinary | Chinese | 250/250 | 353/701 | 1.11 | 0.43-2.84 | 0.92 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.15 | 0.43-3.11 | 0.11 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.78 | 0.66-4.79 | 0.344 |
| Luo et al., 2010 | Urinary | Chinese | 250/250 | 353/701 | 1.11 | 0.43-2.84 | 0.92 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.15 | 0.43-3.11 | 0.11 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.78 | 0.66-4.79 | 0.344 |
| Luo et al., 2010 | Urinary | Chinese | 250/250 | 353/701 | 1.11 | 0.43-2.84 | 0.92 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.15 | 0.43-3.11 | 0.11 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.78 | 0.66-4.79 | 0.344 |
| Luo et al., 2010 | Urinary | Chinese | 250/250 | 353/701 | 1.11 | 0.43-2.84 | 0.92 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.15 | 0.43-3.11 | 0.11 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.78 | 0.66-4.79 | 0.344 |
| Luo et al., 2010 | Urinary | Chinese | 250/250 | 353/701 | 1.11 | 0.43-2.84 | 0.92 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.15 | 0.43-3.11 | 0.11 |
| Luo et al., 2010 | Urinary | Chinese | 59/118 | 59/118 | 1.78 | 0.66-4.79 | 0.344 |
| Study                          | Cases/controls | Effect modifier | OR     | 95% CI          | p-value |
|-------------------------------|----------------|-----------------|--------|-----------------|---------|
| Zheng et al., 2002            |                |                 | 0.63   | 0.38-0.99       | 0.027   |
| Lampe et al., 2007            |                |                 | 1.37   | 0.84-2.22       | 0.175   |
| Iwasaki et al., 2008          |                |                 | 0.48   | 0.29-0.80       | 0.007   |
| Iwasaki et al., 2008          |                |                 | 0.2   | 0.08-0.69       | 0.0001  |
| Goodman et al., 2009          |                |                 | 0.65   | 0.41-1.03       | 0.050   |
| Enoh et al., 2005             |                |                 | 0.66   | 0.47-0.95       | 0.021   |

*OR: Adjusted OR, CI: confidence interval.*
| Bio-marker   | Group                     | Menopausal Status | Post- or Pre-Menopausal | ER+ Status | Odds Ratio | 95% CI         | P for trend |
|-------------|---------------------------|-------------------|-------------------------|------------|------------|---------------|-------------|
| 1234        | American (white)          | Post              |                         |            | 1.32       | 0.70-2.49     | 0.07        |
| 5678        | Dutch                     | Post              |                         |            | 0.87       | 0.55-1.23     | 0.80        |
| 9012        | Japanese-American        | Post              |                         |            | 0.76       | 0.47-1.21     | 0.22        |
| 3456        | American (multiethnic)   | Post              |                         |            | 0.73       | 0.47-1.14     | 0.18        |
| 7890        | Japanese-American        | Pre or peri-Menopausal |             |            | 0.73       | 0.47-1.14     | 0.18        |
| 1012        | Japanese-American        | Post              |                         |            | 0.66       | 0.26-1.65     | 0.34        |
| 2345        | Chinese                   | Post              |                         |            | 0.87       | 0.55-1.38     | 0.55        |
| 6789        | Chinese                   | Post              |                         |            | 0.82       | 0.55-1.23     | 0.39        |
| 4567        | Japanese-American        | Post              |                         |            | 0.76       | 0.47-1.21     | 0.22        |
| 8901        | Japanese-American        | Post              |                         |            | 0.73       | 0.47-1.14     | 0.18        |
| 2345        | Chinese                   | Post              |                         |            | 0.66       | 0.26-1.65     | 0.34        |
| 6789        | Chinese                   | Post              |                         |            | 0.82       | 0.55-1.23     | 0.39        |

Table 3. Continued
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 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 advantages 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 equal-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, 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 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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