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REVIEW ARTICLE

Diet and breast cancer: a systematic review

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Abstract

Breast cancer occurs as a result between genes–diet interactions. Concerning diet, only alcohol is widely recognized for being most consistently associated with breast cancer risk. The purpose of this review is to report through a systematic way the current scientific evidence relating breast cancer and diet, through original-research studies published in English language during the last decade, assessing the consumption of specific foodstuffs/food-nutrients in relation to the disease. The available literature suggests that soy food intake seems to be inversely associated with the disease, while no association seems to be reported for dietary carbohydrates and dietary fiber intake. The consumption of dietary fat, is probably suggestive of an increase in breast cancer risk, while studies evaluating the role of fruit/vegetable, meat as well as dietary patterns and breast cancer risk, provide inconsistent results. Diet seems to be modestly associated with the disease, highlighting the need for more studies to be conducted.

Keywords

Fiber, fruits and vegetables, meat, soy-food

History

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Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in females, worldwide, accounting for 23% (i.e. 1.38 million) of the total new cancer cases and 14% (458 400) of the total cancer deaths in 2008. About half the breast cancer cases and 60% of the deaths are estimated to occur in economically developing countries (Jemal et al., 2011).

Well-established, non-dietary risk factors for breast cancer include hormone replacement therapy and exposure to ionizing radiation especially during puberty and adolescence. The risk is also increased by several reproductive and other factors that are not easily modified including: age (65+ versus <65 years, although risk increases across all ages until age 80), family history of breast cancer, early menarche (<12 years), late menopause (>55 years), late age at first full-term pregnancy and lack of breastfeeding. Moreover, there is consistent evidence that obesity and weight gain during adulthood are associated with an increased risk of breast cancer among post-menopausal (but not pre-menopausal) women (ACS, 2011–2012; WCRF/AICR, 2007).

With respect to diet and breast cancer risk, during the last decades, studies from all over the world have evaluated the relationship between specific foods and some substances they contain with the development of breast cancer (Michels et al., 2007; Romieu, 2011; Thomson, 2012). Among them, only alcohol intake is widely recognized as one of the behaviors most consistently associated with breast cancer risk (WCRF/AICR, 2007). Moreover, the analysis of dietary patterns, an approach that has gained much of interest in modern nutrition epidemiology, instead of the study of specific foods and nutrients, has sparsely been reported in the literature regarding breast cancer development.

The aim of this work was to review and evaluate the current scientific evidence about the relationship between specific foodstuffs (i.e. alcohol, fruits, vegetables, meat, soy food and soy intake) that have been extensively studied in the literature the past years, and breast cancer risk.

Selection of studies

The PRISMA guidelines for reporting systematic reviews were followed here (Moher et al., 2009). In particular, original-research studies that were published in English language during the past decade, between 1 January 2002 and 31 August 2012, were selected through a computer-assisted literature search (i.e. Medline via Pubmed and Scopus). Computer searcher used combinations of key words relating to breast cancer (i.e. breast cancer or breast neoplasm), foodstuffs (i.e. alcohol, fruits, vegetables, meat, soy food and soy intake) or food substances/nutrients they contain (i.e. heterocyclic compounds, amines, dietary fiber, dietary carbohydrate, glycemic index, dietary fat and fatty acids). In addition, the reference lists of the retrieved articles directed the search to relevant present articles that were not allocated through the searching procedure. Only studies published in English have been considered. We have included cohorts and case–control studies, meta-analyses and clinical trials. We excluded studies referring to dietary habits of women during adolescence and to consumption of supplements. The endpoint was only breast cancer incidence and not recurrence or survival. At this point, it should be mentioned that reading carefully the existing literature, and based on the great diversity among studies regarding the way they have evaluated exposure dietary factors

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and outcomes, a potential attempt to metanalyze their findings through a quantitative way would lead to un-robust combined effect estimates, with unpredictable sources of heterogeneity; therefore, it was decided to present, with a systematic manner, only their findings and not a combined effect.

Studies on diet and breast cancer

Alcohol consumption

Among the dietary factors, alcohol intake is widely recognized as one of the behaviors most consistently associated with increased breast cancer risk, independently of the type of alcoholic drink consumed and of menopausal status (WCRF/AICR, 2007). Since, the early 1980s numerous studies have examined this link. In a recent published review of 113 papers reporting breast cancer risk estimates for light drinkers, Seitz et al. (2012) analyzed 44 552 cases in the reference category of non-drinkers and 77 539 cases in the light drinkers' category. First, they reported a modest but significant association between light drinking and breast cancer. Moreover, the results of their meta-analysis consistently indicated a 40–50% elevated risk of breast cancer in women consuming three or more alcoholic drinks/day. Finally, they also observed consistent evidence for a positive dose-risk relation between alcohol drinking and breast cancer.

In this review, we included 27 studies, 7 case–controls and 20 cohorts, which analyze the relationship between alcohol consumption and breast cancer risk (Table 1). The smallest study included $n = 556$ women (Lenz et al., 2002) whereas the largest study included $n = 274\,688$ women (Tjonneland et al., 2007). Only 1 out of the 27 studies reported no overall effect of alcohol consumption on breast cancer. In particular, Kawai et al. (2011) in the Miyagi cohort study, followed up a total of 19 227 women aged 40–64 years old to evaluate the associations of alcohol consumption with breast cancer risk in a Japanese population. Their study revealed that breast cancer risk was not associated with the amount of alcohol consumed per occasion or per day. Possible explanations for this result include firstly the fact that Japanese women probably have lifestyle factors that differ from those of women in Western countries, and secondly differences in distribution of exposure and confounding variables among study areas that may have affected the risk. Finally, the above result could be also explained by the presence of an unmeasured mechanism such as a gene polymorphism.

In contrast, the majority of the studies included in this review showed that modest or high alcohol consumption was associated with a moderate increase in breast cancer risk (Allen et al., 2009; Beasley et al., 2010; Berstad et al., 2008; Chen et al., 2011; Deandrea et al., 2008; Duffy et al., 2009; Feigelson et al., 2003; Horn-Ross et al., 2004; Kabat et al., 2011; Lenz et al., 2002; Lew et al., 2009; Li et al., 2003, 2009, 2010; Lin et al., 2005; Mattisson et al., 2004b; Mccarty et al., 2012; Morch et al., 2007; Petri et al., 2004; Stolzenberg-Solomon et al., 2006; Suzuki et al., 2005, 2010; Tjonneland et al., 2006, 2007; Zhang & Holman, 2011; Zhang et al., 2007).

Several of the above studies examined also the association of alcohol consumption with breast cancer risk defined by estrogen receptor (ER) and progesterone receptor (PR) status and reported an increased risk of ER^+ (Chen et al., 2011; Deandrea et al., 2008; Kabat et al., 2011; Lew et al., 2009; Suzuki et al., 2005), ER^+/PR^+ (Deandrea et al., 2008; Lew et al., 2009; Li et al., 2003, 2010; Suzuki et al., 2005; Zhang et al., 2007) and even PR^+ (Chen et al., 2011; Lew et al., 2009) breast cancers, further supporting the hypothesis that alcohol influences hormonal status through hormone-related mechanisms (such as increased estrogen and androgen levels; Singletary & Gapstur 2001) leading to increased breast cancer risk.

The mechanisms by which alcohol stimulates breast carcinogenesis are still not understood. Increased estrogen levels in women consuming alcohol appear to be the first mechanism underlying the association. In fact, during alcohol consumption, increased estrogen concentrations may be observed by many ways, including: (a) increased aromatase activity which leads to conversion of testosterone to estrogens, (b) inhibition of the activity of two enzymes important in estrogen degradation, (c) decreased melatonin secretion which inhibits estrogen production and (d) increase in the hepatic redox state resulting in the decrease of steroid metabolism. As a result, estrogens may exert their carcinogenic effect on breast tissue either via the ER or directly (Seitz et al., 2012). Moreover, products of alcohol metabolism, like acetaldehyde and free radicals, have been implicated to their role in alcohol-associated carcinogenesis, as they seem to cause DNA damages (Coronado et al., 2011; Dumitrescu & Shields, 2005; Seitz et al., 2012). Finally, the association between alcohol consumption and breast cancer risk may be modified, at least in part, by alcohol's interference with the absorption of folate. Alcohol is a known folate antagonist and folate is a micronutrient known to be important in DNA synthesis and repair and in neutralizing ROS (reactive oxygen species) which are products of alcohol metabolism. With regard to one-carbon metabolism and according to the above pathway, alcohol consumption can negatively affect folate levels and as a result, folate perturbation can disturb DNA methylation and DNA synthesis, which is important in carcinogenesis (Coronado et al., 2011; Dumitrescu & Shields, 2005; Zhang et al., 1999). Other mechanisms including epigenetics or retinoid concentrations remain unclear and for this reason need further investigation (Seitz et al., 2012).

Fruits and vegetables

Fruits and vegetables contain a wide range of constituents which may have cancer-preventing effects including antioxidant vitamins like vitamin C and vitamin E, folate, dietary fiber, dithiolthiones, glucosinolates, indoles, isothiocyanates, protease inhibitors and phytochemicals (lycopene, phenolic compounds, flavonoids etc.) (Steinmetz & Potter 1991, 1996). For this reason, the association between fruits, vegetables and breast cancer risk is of great interest. However, according to the 2007 WCRF/AICR Second Expert Report (WCRF/AICR, 2007) followed by the Updated Breast Cancer 2010 Report (WCRF/AICR, 2010), the evidence of fruits and vegetables consumption in relation to breast cancer incidence, are limited and no conclusions can be reached.

In this review, we included 11 studies investigating the association between fruits, vegetables and breast cancer risk (Table 2). Nine of them were case–controls, while the remaining two studies were cohorts that both showed no significant associations (Boggs et al., 2010; van Gils et al., 2005). In fact, in 2005, the EPIC working group reported no significant associations between intake of total vegetable and fruit groups and breast cancer risk, in 3659 invasive incident breast cancer cases among 285 526 women after 5.4 years of follow-up (van Gils et al., 2005). More recently, *Boggs and his partners*, during 12 years of follow-up, reported 1268 incident cases of breast cancer among 51 928 women who participated in the Black Women's Health Study. They observed that total fruit, total vegetable and total fruit and vegetable intakes were not significantly associated with breast cancer risk overall (Boggs et al., 2010). Similar results were observed from Malin et al. (2003) as well as Do et al. (2007) in two case–control studies that were conducted in Chinese and Korean women, respectively.

In contrast, the majority of the case–control studies conducted in the last decade have observed significant and inverse associations between total fruit and vegetable intake and breast cancer

Table 1. Studies on alcohol intake and breast cancer risk from 2002.

References	Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/ Frequency of alcohol consumption	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
Feigelson et al. (2003)	Cohort	66 561/1303 5 years	Overall	Highest category versus non-users (15 or more grams of ethanol per day versus none)	RR = 1.26 (1.04–1.53)	Age, ethanol, dietary folate, methionine, multivitamin use, race, education, first-degree family history of breast cancer, history of breast lump, mammographic history, HRT use, parity and age at first birth, age at menopause, age at menarche, physical activity, BMI, adult weight gain, and energy.
Li et al. (2003)	Case–control	975/1007	Overall	Ever-users versus non-users	OR = 1.30 (1.00–1.50)	Age, family history of breast cancer, body mass index.
				Highest category versus non-users (30 or more grams of alcohol per day versus never)	OR = 1.70 (1.10–2.60)	
			Ductal Cancer	Ever-users versus non-users	OR = 1.20 (0.90–1.40)	
				Highest category versus non-users (30 or more grams of alcohol per day versus never)	OR = 1.50 (0.90–2.30)	
			Lobular Cancer	Ever-users versus non-users	OR = 1.80 (1.30–2.50)	
				Highest category versus non-users (30 or more grams of alcohol per day versus never)	OR = 2.60 (1.30–4.90)	
Horn-Ross et al. (2004)	Cohort	103 460/1742	*Alcohol consumption – past year*			Age, race/ethnicity, caloric intake, family history of breast cancer, age at menarche, nulliparity/age at FFTP, physical activity, BMI, and duration of ERT use.
			Pre-/peri-menopausal women	Highest category versus non-drinkers (20 or more grams of alcohol per day versus never)	RR = 1.21 (0.76–1.92)	
			Post-menopausal women	Highest category versus non-drinkers (20 or more grams of alcohol per day versus never)	RR = 1.32 (1.06–1.63)	
Mattisson et al. (2004a)	Cohort	11 726/342 mean 7.6 years	Total Alcohol consumption	Highest category versus abstainers (more than 30 grams of alcohol per day versus abstainers)	IRR = 1.68 (0.91–3.12)	Diet interviewer, method version, season of diet interview, age at baseline, TE, change of dietary habits, height, waist, current hormone use, age at birth of first child, age at menarche, leisure time physical activity, smoking habits, educational level.
			Wine consumption	Highest category versus abstainers (more than 20.8 cl of ine per day versus abstainers)	IRR = 2.12 (1.24–3.60)	
Petri et al. (2004)	Cohort	13 074/473	Pre-menopausal women	Highest category versus lowest category of total alcohol intake (>27 versus 1–6 drinks per week)	RR = 3.49 (1.36–8.99)	Age, cohort, parity and use of HRT.
			Post-menopausal women (all)	Highest category versus lowest category of total alcohol intake (>27 versus 1–6 drinks per week)	RR = 0.57 (0.18–1.78)	

(*continued*)

Table 1. Continued

References	Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/ Frequency of alcohol consumption	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
			Both pre- and post-menopausal women	Highest category versus lowest category of total alcohol intake (>27 versus 1–6 drinks per week)	RR = 1.19 (0.58–2.41)	
Lin et al. (2005)	Cohort	35 844/151 7.6 years	Overall	Highest category versus lowest category of alcohol consumption (15 or more grams of alcohol per day versus non-drinkers)	RR = 2.93 (1.55–5.54)	Age, BMI, study area, family history of breast cancer, walking, use of hormone, age at menarche, age at first birth, age at menopause and number of births.
Suzuki et al. (2005)	Cohort	51 847/1188 8.3 years	All invasive tumors	Highest category versus lowest category of alcohol consumption (10 or more grams of ethanol per day versus non-drinkers)	RR = 1.43 (1.16–1.76)	Age, body mass index, height, education, parity, age at first birth, age at menarche, age at menopause, type of menopause, use of oral. Contraceptives, use of postmenopausal hormones, first-degree of family history of breast cancer, history of benign breast disease, quartiles of total energy intake, energy-adjusted dietary fiber and total fat intake.
			ER^+/PR^+ tumors	Highest category versus lowest category of alcohol consumption (10 or more grams of ethanol per day versus non-drinkers)	RR = 1.35 (1.02–1.80)	
			ER^+/PR^- tumors	Highest category versus lowest category of alcohol consumption (10 or more grams of ethanol per day versus non-drinkers)	RR = 2.36 (1.56–3.56)	
			ER^-/PR^+ tumors	Highest category versus lowest category of alcohol consumption (10 or more grams of ethanol per day versus non-drinkers)	RR = 0.62 (0.13–2.90)	
			ER^-/PR^- tumors	Highest category versus lowest category of alcohol consumption (10 or more grams of ethanol per day versus non-drinkers)	RR = 0.80 (0.38–1.67)	
Stolzenberg-Solomon et al. (2006)	Randomized multicenter trial	25 400/691 median 4.94 years	Overall	Highest versus lowest quintile (more than 7.62 versus 0.01 or less grams of alcohol per day)	HR = 1.37 (1.08–1.76)	Education.
Zhang et al. (2007)	Cohort	38 454/1484 10 years	Invasive and in situ tumors	Highest category versus lowest category of alcohol consumption (30 or more grams of alcohol per day versus non-drinkers)	RR = 1.32 (0.96–1.82)	Age, randomized treatment assignment, age at menarche, age at first pregnancy lasting ≥6 months, number of pregnancies lasting ≥6 months, menopausal status, age at menopause, post-menopausal hormone use, body mass index, family history of breast cancer in the mother or a sister, history of benign breast disease, physical activity, multivitamin supplement use, and total energy intake
			Invasive tumors	Highest category versus lowest category of alcohol consumption (30 or more grams of alcohol per day versus non-drinkers)	RR = 1.43 (1.02–2.02)	
			ER^+/PR^+ tumors	Highest category versus lowest category of alcohol consumption (30 or more grams of alcohol per day versus non-drinkers)	RR = 1.39 (0.90–2.15)	
			ER^+/PR^- tumors	Highest category versus lowest category of alcohol consumption (30 or more grams of alcohol per day versus non-drinkers)	RR = 0.69 (0.17–2.88)	

			ER^-/PR^- tumors	Highest category versus lowest category of alcohol consumption (30 or more grams of alcohol per day versus non-drinkers)	RR = 1.15 (0.41–3.19)	
Morch et al. (2007)	Cohort	17 647/457 8 years	Overall	Highest category versus lowest category of alcohol consumption (more than 27 drinks per week versus 1–3 drinks per week)	RR = 1.62 (1.04–2.52)	Age, age at birth of first child, menarche, relatives with breast cancer and self reported benign breast disease.
Tjonneland et al. (2007)	Cohort	274 688/4285 6.4 years	Overall	Highest category versus lowest category of alcohol consumption (more than 19 g of alcohol per day versus > 0 to 1.5 g of alcohol per day)	IRR = 1.13 (1.01–1.25)	Height, weight, age at menarche, parity, current oral contraceptive use, current use of hormone replacement therapy, menopausal status, smoking status and education.
Berstad et al. (2008)	Case–control	1728/435	Recent alcohol intake (average intake in the 5 years before the alcohol reference date)	Highest category versus lowest category of alcohol consumption (more than 14 alcoholic drinks per week versus never drinkers)	OR = 1.82 (1.01–3.28)	Age, race, education, first-degree breast cancer family history, age at menarche, age at first full-term pregnancy, parity, breast-feeding. Duration, smoking and BMI.
Deandrea et al. (2008)	Case–control	989/1350	ER^-	Highest category versus lowest category of alcohol consumption (13.8 or more grams of ethanol per day versus never drinkers)	OR = 1.36 (0.93–2.01)	Age, center, education, parity, menopausal status, age at menarche, family history of breast cancer, BMI, and energy intake.
			ER^+	Highest category versus lowest category of alcohol consumption (13.8 or more grams of ethanol per day versus never drinkers)	OR = 2.16 (1.68–2.76)	
			ER^-/PR^-	Highest category versus lowest category of alcohol consumption (13.8 or more grams of ethanol per day versus never drinkers)	OR = 1.25 (0.81–1.94)	
			ER^+/PR^-	Highest category versus lowest category of alcohol consumption (13.8 or more grams of ethanol per day versus never drinkers)	OR = 1.30 (0.76–2.24)	
			ER^-/PR^+	Highest category versus lowest category of alcohol consumption (13.8 or more grams of ethanol per day versus never drinkers)	OR = 1.72 (0.83–3.59)	
			ER^+/PR^+	Highest category versus lowest category of alcohol consumption (13.8 or more grams of ethanol per day versus never drinkers)	OR = 2.34 (1.81–3.04)	
Allen et al. (2009)	Cohort	1 280 296/28 380 3 years	Overall	Highest category versus lowest category of alcohol intake (15 or more drinks per week versus non-drinkers)	RR = 1.29 (1.23–1.35)	Age, region of residence, socio-economic status, body mass index, smoking, physical activity, use of oral contraceptives, and hormone replacement therapy.

(*continued*)

Table 1. Continued

References	Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/ Frequency of alcohol consumption	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
Duffy et al. (2009)	Cohort	88 530/1783 5 years	Post-menopausal women	Highest category versus lowest category of alcohol intake (more than 15 g of alcohol per day versus none)	HR = 1.13 (0.96–1.32)	Race/ethnicity, income and education, tobacco consumption, BMI, history of breast biopsy, number of pregnancies, ever breast fed, family history, previous combined HRT use, age at menarche, age at menopause, weekly METs.
Lew et al. (2009)	Cohort	184 418/5461 7 years	Total breast cancer	Highest category versus lowest category of alcohol intake (more than 35 g of alcohol per day versus 0)	RR = 1.35 (1.17–1.56)	Race, height, body mass index, age at birth of first child and number of children, family history of breast cancer, age at menopause, physical activity, smoking, past oral contraceptive use, menopausal hormone therapy use, number of breast biopsies, and intakes of total folate, total fat and total energy.
			Ductal tumors	Highest category versus lowest category of alcohol intake (more than 35 g of alcohol per day versus 0)	RR = 1.46 (1.22–1.75)	
			Lobular tumors	Highest category versus lowest category of alcohol intake (more than 35 g of alcohol per day versus 0)	RR = 1.52 (0.95–2.44)	
			Ductal-lobular tumors	Highest category versus lowest category of alcohol intake (more than 35 g of alcohol per day versus 0)	RR = 1.21 (0.66–2.20)	
			Other tumors	Highest category versus lowest category of alcohol intake (more than 35 g of alcohol per day versus 0)	RR = 1.01 (0.71–1.43)	
Li et al. (2009)	Cohort	70 033/2829 mean 16 years	Overall	Highest category versus lowest category of alcohol intake (3 or more drinks per day versus never drinkers)	RR = 1.40 (1.10–1.70)	Age, ethnicity, education, body mass index, marital status, smoking alcohol, history of any breast surgery, family history and parity.
			ER^+	Highest category versus lowest category of alcohol intake (3 or more drinks per day versus never drinkers)	RR = 1.70 (1.20–2.30)	
			ER^-	Highest category versus lowest category of alcohol intake (3 or more drinks per day versus never drinkers)	RR = 0.80 (0.30–1.80)	
			ER unknown	Highest category versus lowest category of alcohol intake (3 or more drinks per day versus never drinkers)	RR = 1.30 (1.00–1.70)	
			PR^+	Highest category versus lowest category of alcohol intake (3 or more drinks per day versus never drinkers)	RR = 1.60 (1.10–2.30)	
			PR^-	Highest category versus lowest category of alcohol intake (3 or more drinks per day versus never drinkers)	RR = 1.20 (0.70–2.10)	
			PR unknown	Highest category versus lowest category of alcohol intake (3 or more drinks per day versus never drinkers)	RR = 1.20 (0.70–2.10)	
			Both positive	Highest category versus lowest category of alcohol intake (3 or more drinks per day versus never drinkers)	RR = 1.70 (1.20–2.50)	

			Both negative	Highest category versus lowest category of alcohol intake (3 or more drinks per day versus never drinkers)	RR = 0.70 (0.30–1.80)	
			ER^+/PR^-	Highest category versus lowest category of alcohol intake (3 or more drinks per day versus never drinkers)	RR = 1.70 (0.90–3.40)	
			PR^+/ER^-	Highest category versus lowest category of alcohol intake (3 or more drinks per day versus never drinkers)	RR = 0.70 (0.10–6.50)	
			Both unknown	Highest category versus lowest category of alcohol intake (3 or more drinks per day versus never drinkers)	RR = 1.30 (1.00–1.70)	
Beasley et al. (2010)	Case–control	1000/1074	Lifetime alcohol use	Highest category versus lowest category of alcohol intake (ever drinkers versus non-drinkers)	OR = 1.25 (0.99–1.58)	Age, region, health care institution, BMI, family history of breast cancer, age at first pregnancy, number of births, lactation, energy intake, physical activity, education, age at menarche, menopausal status, OC, smoking, fibrocystic disease, hormone therapy.
Li et al. (2010)	Cohort	87 724/2944	All invasive cancers	Highest category versus lowest category of alcohol intake (14 or more drinks per week versus never drinkers)	RR = 1.24 (1.00–1.55)	Age, race/ethnicity, education, body mass index, hormone therapy use, smoking status, Gail model 5-year risk of breast cancer, first-degree family history of breast cancer, parity, and number of mammograms in the past 5-years.
			Invasive ductal carcinoma	Highest category versus lowest category of alcohol intake (14 or more drinks per week versus never drinkers)	RR = 1.04 (0.78–1.39)	
			Invasive lobular carcinoma	Highest category versus lowest category of alcohol intake (14 or more drinks per week versus never drinkers)	RR = 2.13 (1.36–3.33)	
			Invasive ER^+/PR^+ cancers	Highest category versus lowest category of alcohol intake (14 or more drinks per week versus never drinkers)	RR = 1.27 (0.96–1.68)	
			Invasive ER^+/PR^- cancers	Highest category versus lowest category of alcohol intake (14 or more drinks per week versus never drinkers)	RR = 1.45 (0.80–2.63)	
			Invasive ER^-/PR^- cancers	Highest category versus lowest category of alcohol intake (14 or more drinks per week versus never drinkers)	RR = 0.46 (0.19–1.12)	
			Invasive ER^+/PR^+ ductal cancers	Highest category versus lowest category of alcohol intake (7 or more drinks per week versus never drinkers)	RR = 1.14 (0.87–1.50)	
			Invasive ER^+/PR^+ lobular cancers	Highest category versus lowest category of alcohol intake (7 or more drinks per week versus never drinkers)	RR = 1.82 (1.18–2.81)	
Suzuki et al. (2010)	Cohort	50 757/572 average 13.8 years	Overall	Highest category versus lowest category of alcohol intake (>150 g of ethanol per week versus never drinkers)	RR = 1.75 (1.16–2.65)	Age time-scales, area, height, BMI, smoking status, leisure-time physical activity, age at menarche, age at first-birth, parity, age at menopause, use of exogenous female hormones,
			All ER^+	Highest category versus lowest category of alcohol intake (>150 g of ethanol per week versus never drinkers)	RR = 1.58 (0.72–3.48)	

(*continued*)

Table 1. Continued

References	Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/ Frequency of alcohol consumption	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
			ER^+/PR^+	Highest category versus lowest category of alcohol intake (>150 g of ethanol per week versus never drinkers)	RR = 2.09 (0.88–4.97)	energy-adjusted intake of isoflavones.
			ER^+/PR^-	Highest category versus lowest category of alcohol intake (>150 g of ethanol per week versus never drinkers)	Not reported	
			All ER^-	Highest category versus lowest category of alcohol intake (>150 g of ethanol per week versus never drinkers)	Not reported	
			ER^-/PR^-	Highest category versus lowest category of alcohol intake (>150 g of ethanol per week versus never drinkers)	Not reported	
Zhang & Holman (2011)	Case–control	1009/1009	All women	(>0 to <5 g of ethanol per day versus 0)	OR = 0.56 (0.45–0.69)	Age at interview, education, BMI, oral contraceptive use, hormone replacement therapy, breast cancer in first-degree relatives, total energy intake, folate intake, tea drinking and menopausal status.
			Pre-menopausal	(>0 to <5 g of ethanol per day versus 0)	OR = 0.62 (0.48–0.79)	
			Post-menopausal	(>0 to <5 g of ethanol per day versus 0)	OR = 0.41 (0.27–0.62)	
			All women			
			ER^+	(>0 to <15 g of ethanol per day versus 0)	OR = 0.62 (0.48–0.81)	
			ER^-	(>0 to <15 g of ethanol per day versus 0)	OR = 0.52 (0.38–0.70)	
			PR^+	(>0 to <15 g of ethanol per day versus 0)	OR = 0.58 (0.44–0.76)	
			PR^-	(>0 to <15 g of ethanol per day versus 0)	OR = 0.56 (0.42–0.75)	
			ER^+/PR^+	(>0 to <15 g of ethanol per day versus 0)	OR = 0.55 (0.41–0.73)	
			ER^-/PR^-	(>0 to <15 g of ethanol per day versus 0)	OR = 0.46 (0.33–0.64)	
			ER^+/PR^- or ER^-/PR^+	(>0 to <15 g of ethanol per day versus 0)	OR = 1.06 (0.68–1.64)	
Kabat et al. (2011)	Cohort	146 985/5430 median 8 years	TNBC	Highest category versus lowest category of alcohol intake (7 or more drinks per week versus never drinkers)	RR = 0.57 (0.34–0.95)	Age, education, ethnicity, body mass index, waist circumference, oral contraceptive use, hormone therapy, age at menarche, age at first birth, age at menopause, alcohol, pack-years of smoking, family history of breast cancer, history of breast biopsy, mammogram with past 2 years, physical activity, and treatment/control arm assignment in the estrogen alone, estrogen plus progestin, calcium plus vitamin D, and dietary modification trials.
			ER^+	Highest category versus lowest category of alcohol intake (7 or more drinks per week versus never drinkers)	RR = 1.26 (1.06–1.50)	
Chen et al. (2011)	Cohort	105 986/7690 2.4 million person-years	*All invasive breast cancers*			Age, questionnaire year, ages at menarche and menopause, family history of breast cancer in first degree relative, benign breast disease, body mass index,
			Baseline intake	(5–9.9 g of alcohol per day versus 0)	RR = 1.15 (1.06–1.26)	
			Current updated intake	(5–9.9 g of alcohol per day versus 0)	RR = 1.11 (1.01–1.20)	
			Cumulative intake	(5–9.9 g of alcohol per day versus 0)	RR = 1.15 (1.06–1.24)	

						parity and age at first full term birth, hormone therapy use, total duration of breastfeeding, and cigarette smoking.
Kawai et al. (2011)	Cohort	19 227/241 13 years	Alcohol drinking frequency	Highest category versus lowest category of alcohol intake (5–7 times per week versus never)	RR = 0.65 (0.28–1.49)	Age, body mass index, smoking, occupation, walking, educational level, age at menarche, parity number, family history of breast cancer, age at menopause, use of exogenous female hormones and/or OC, energy-adjusted intakes of fat and folate and energy intake.
			Alcohol drinking-amount per day	Highest category versus lowest category of alcohol intake (15 or more grams of alcohol per day versus never)	RR = 0.87 (0.40–1.91)	
Mccarty et al. (2012)	Multi-center trial	38 660/1041(1070)	Daily servings of alcohol	Highest category versus lowest category of alcohol intake (3 or more drinks per day versus none)	OR = 2.00 (1.11–3.61)	Age at baseline, year of baseline, race and ethnicity, age at menarche, age at menopause, parity, age at first live birth, family history of breast cancer, personal history of benign breast disease.

risk (Aune et al., 2009a; Gaudet et al., 2004; Lima et al., 2008; Lissowska et al., 2008; Masala et al., 2012; Shannon et al., 2005; Zhang et al., 2009b). In some of them, the correlation appears to be stronger for fruits compared with vegetables (Aune et al., 2009a; Lima et al., 2008; Lissowska et al., 2008) which should be taken into account as it could further contribute to the explanation of the association with breast cancer risk. Fruits are usually eaten raw, while vegetables may be consumed both cooked and raw and it is possible that some of the beneficial constituents of vegetables get destroyed during cooking (like digestive enzymes) or their availability is changed, and this may be part of the reason for the different results between fruits and vegetables in some studies (Link & Potter, 2004). Finally, it should also be taken into account that each study refers to different group/groups of fruits and/or vegetables (i.e. cruciferous vegetables, leafy and dark-green leafy vegetables and yellow-orange vegetables) each of which contains different constituents (i.e. glucosinolates, indoles and isothiocyanates in cruciferous vegetables, carotenes and folate in leafy vegetables) and as a consequence differences in results can be also attributed to the aforementioned consideration.

Meat intake

The evidence that red meats and processed meats are a cause of colorectal cancer is convincing according to the 2007 WCRF/AICR report (WCRF/AICR, 2007). On the other hand, regarding breast cancer, the results of the studies remain inconsistent with both positive and negative associations being reported. We analyzed 14 studies conducted the last 10 years (Aune et al., 2009b; Cho et al., 2006; Egeberg et al., 2008; Ferrucci et al., 2009; Fu et al., 2011; Holmes et al., 2003; Kabat et al., 2009; Larsson et al., 2009b; Lima et al., 2008; Mignone et al., 2009; Pala et al., 2009; Sonestedt et al., 2008; Taylor et al., 2007; Zhang et al., 2009c) including six case–control and eight cohort studies (Table 3). The smallest study included $n = 183$ women (Lima et al., 2008), whereas the largest study included $n = 319\,826$ women (Pala et al., 2009). The age range of the studies varied between 20 and 80 years old. Seven of them reported a positive association (Aune et al., 2009b; Cho et al., 2006; Egeberg et al., 2008; Ferrucci et al., 2009; Fu et al., 2011; Lima et al., 2008; Taylor et al., 2007) while the other seven (Holmes et al., 2003; Kabat et al., 2009; Larsson et al., 2009b; Mignone et al., 2009; Pala et al., 2009; Sonestedt et al., 2008; Zhang et al., 2009c) found no significant association between total or red meat intake and breast cancer risk.

Among the aforementioned studies, there is one who specifically highlighted the fact that breast tumors are often characterized by hormone (estrogen and progesterone) receptor status. In this one, Cho et al. (2006) assessed red meat intake and breast cancer risk in 90 569 pre-menopausal women aged 26–46 years old who participated in the Nurses' Health Study II. During the 12-year follow-up, they observed that red meat intake was strongly related to elevated risk of breast cancers that were estrogen and progesterone receptor positive (ER^+/PR^+; $n = 512$). Furthermore, in a cohort study conducted in Sweden, Larsson et al. (2009b) although their results did not support an association between red meat intake and overall breast cancer risk, they suggested that fried meat intake may increase the risk of ER^+/PR^- breast cancer.

Several potential mechanisms could explain the association between meat intake and increased breast cancer risk. First, heterocyclic amines (HA) and polycyclic aromatic hydrocarbons (PAH) are formed during cooking and grilling of meats. These substances seem to increase mammary tumors in animals and have been hypothesized to increase also breast cancer risk

Table 2. Studies on fruits and vegetables intake and breast cancer risk from 2002.

References	Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/ Group of fruits/ vegetables	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
Malin et al. (2003)	Case–control	1459/1556	Total vegetable	Highest versus lowest quintile (369.6 g/day versus 0)	OR = 1.05 (0.81–1.40)	Age, education, family history of breast cancer, history of breast fibroadenoma, waist-to-hip ratio, menarche age, physical activity, ever had live birth, age at first live birth, and total energy compared to the lowest quintile group.
			Dark green vegetables (other than bok choy)	Highest versus lowest quintile (18.1 g/day versus 0)	OR = 0.65 (0.51–0.83)	
			Dark yellow vegetables	Highest versus lowest quintile (7.5 g/day versus 0)	OR = 0.79 (0.60–0.98)	
			Total fruits without watermelon	Highest versus lowest quintile (225.9 g/day versus 0)	OR = 0.77 (0.60–0.98)	
Gaudet et al. (2004)	Case–control	1463/1500	*Post-menopausal*			
			Any fruits, fruit juices and vegetables	Highest fifth of intake versus lowest fifth of intake	OR = 0.72 (0.53–0.99)	Age at reference date, dietary energy intake, menopausal status, active and passive smoking, lifetime alcohol intake, menopausal status, physical activity from menarche to reference date, family history of cancer, season of interview, education, use of oral contraceptives, use of hormone replacement therapy, lactation, race, age at first birth, parity, body mass index at reference, body mass index at age 20 years, and single and multiple vitamin supplements.
			Any vegetables	Highest fifth of intake versus lowest fifth of intake	OR = 0.63 (0.46–0.86)	
			Leafy vegetables	Highest fifth of intake versus lowest fifth of intake	OR = 0.66 (0.50–0.86)	
			Yellow vegetables	Highest fifth of intake versus lowest fifth of intake	OR = 0.78 (0.58–1.03)	
			ER^+/PR^+			
			Any fruits, fruit juices and vegetables	Highest fifth of intake versus lowest fifth of intake	OR = 0.64 (0.49–0.83)	
			Any vegetables	Highest fifth of intake versus lowest fifth of intake	OR = 0.79 (0.61–1.03)	
			Leafy vegetables	Highest fifth of intake versus lowest fifth of intake	OR = 0.70 (0.53–0.92)	
			Yellow vegetables	Highest fifth of intake versus lowest fifth of intake	OR = 0.64 (0.49–0.84)	
van Gils et al. (2005)	Cohort	285 526/3659 median 5.4 years	Total vegetables	Highest versus lowest quintile (>309 g/day versus ≤109 g/day)	RR = 0.98 (0.84–1.14)	Energy intake divided into energy from fat and energy from nonfat sources, alcohol intake, saturated fat intake, height, weight, age at menarche, parity, current oral contraceptive use, current use of hormone therapy, menopausal status, smoking status, physical activity and education.
			Total fruits	Highest versus lowest quintile (>367 g/day versus ≤114 g/day)	RR = 1.09 (0.94–1.25)	
			Fruit and vegetable juices	Highest versus lowest quintile (>120 g/day versus 0 g/day)	RR = 1.05 (0.92–1.20)	
Shannon et al. (2005)	Case–control	378/1070	Total fruit and vegetable	Highest versus lowest quartile (≥3.8 servings/day versus ≤2.3 servings/day)	OR = 0.48 (0.29–0.78)	Age, total energy intake, and breast-feeding.
			Fruit	Highest versus lowest quartile (≥1.2 servings/day versus ≤3.9 servings/week)	OR = 0.34 (0.21–0.55)	
			Vegetable	Highest versus lowest quartile (≥2.6 servings/day versus ≤1.5 servings/day)	OR = 0.60 (0.38–0.94)	

Do et al. (2007)	Case–control	359/708	Total fruits	Highest versus lowest quartile (>192.01 g/day versus <82.28 g/day)	OR = 0.79 (0.52–1.32)	Age, education, income, age at menarche, parity, age at first live birth, history of breastfeeding, use of hormones (oral contraceptives and hormone replacement), family history of breast cancer in a first-degree relative, frequency of exercise, physical activity, cigarette smoking, and alcohol consumption.
			Total vegetables	Highest versus lowest quartile (>193.24 g/day versus <65.49 g/day)	OR = 0.76 (0.46–1.23)	
Lima et al. (2008)	Case–control	89/94	Fruits and juices	Highest versus lowest category of intake (>21.7 portions/week versus ≤14.7 portions/week)	OR = 0.02 (0.01–0.12)	Age group, origin, oral contraceptives, age at menopause, body mass index, and energy.
			Vegetables	Highest versus lowest category of intake (>20.3 portions/week versus ≤11.2 portions/week)	OR = 1.37 (0.48–3.95)	
Lissowska et al. (2008)	Case–control	2386/2503	*All women*			Age, study site, education, age at menarche, number of full-term birth, age at full-term birth, menopausal status, age at menopause, BMI, family history of breast cancer, benign biopsy, oral contraceptive use, HRT, alcohol, total caloric intake.
			Total fruit	Highest versus lowest quartile (>293.2 g/day versus ≤131.5 g/day)	OR = 0.76 (0.63–0.91)	
			Total vegetable	Highest versus lowest quartile (>548.0 g/day versus ≤380.1 g/day)	OR = 1.13 (0.93–1.37)	
			Pre-menopausal			
			Total fruit	Highest versus lowest quartile (>293.2 g/day versus ≤131.5g/day)	OR = 1.10 (0.78–1.55)	
			Total vegetable	Highest versus lowest quartile (>548.0 g/day versus ≤380.1 g/day)	OR = 1.09 (0.77–1.54)	
			Post-menopausal			
			Total fruit	Highest versus lowest quartile (>293.2 g/day versus ≤131.5 g/day)	OR = 0.66 (0.53–0.84)	
			Total vegetable	Highest versus lowest quartile (>548.0 g/day versus ≤380.1 g/day)	OR = 0.99 (0.78–1.26)	
			ER^+			
			Total fruit	Highest versus lowest quartile (>293.2 g/day versus ≤131.5 g/day)	OR = 0.69 (0.54–0.88)	
			ER^-			
			Total fruit	Highest versus lowest quartile (>293.2 g/day versus ≤131.5 g/day)	OR = 0.89 (0.67–1.19)	
Aune et al. (2009a)	Case–control	3539/2032	Total fruit and vegetables	Highest versus lowest category of intake (>380 g/day versus 0–220 g/day)	OR = 0.47 (0.31–0.71)	Age, sex, residence, income, interviewer, education, smoking status, age at starting smoking, age at quitting smoking, cigarettes per day, alcohol, total meat, grains, fatty foods (eggs, butter, cheese, custard, desserts), mate drinking status, total energy intake and BMI. Fruit and vegetable intakes mutually adjusted.
			Total fruit	Highest versus lowest category of intake (>160 g/day versus 0–80 g/day)	OR = 0.60 (0.42–0.87)	
			Total vegetables	Highest versus lowest category of intake (>200 g/day versus 0–100 g/day)	OR = 0.53 (0.35–0.81)	
Zhang et al. (2009b)	Case–control	438/438	Total vegetables	Highest versus lowest quartile	OR = 0.28 (0.18–0.43)	Age at menarche, BMI, history of benign breast disease, mother/sister/daughter with breast cancer, physical activity, passive smoking and total energy intake.
			Total fruits	Highest versus lowest quartile	OR = 0.53 (0.34–0.82)	

(*continued*)

Table 2. Continued

References	Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/ Group of fruits/ vegetables	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
Boggs et al. (2010)	Cohort	51 928/1268 12 years	*All women*			Age, energy intake, age at menarche, body mass index at age 18 years, family history of breast cancer, education, geographic region, parity, age at first birth, oral contraceptive use, menopausal status, age at menopause, menopausal hormone use, vigorous activity, smoking status, alcohol intake, and multivitamin use.
			Total fruits and vegetables	Highest versus lowest category of intake (≥4 servings/day versus <1 serving/day)	IRR = 0.87 (0.71–1.07)	
			Total vegetables	Highest versus lowest category of intake (≥2 servings/day versus <4 servings/week)	IRR = 0.87 (0.73–1.05)	
			Total fruits	Highest versus lowest category of intake (≥2 servings/day versus <2 servings/week)	IRR = 0.91 (0.74–1.11)	
			Pre-menopausal women			
			Total fruits and vegetables	Highest versus lowest category of intake (≥4 servings/day versus <1 serving/day)	IRR = 0.90 (0.65–1.23)	
			Total vegetables	Highest versus lowest category of intake (≥2 servings/day versus <4 servings/week)	IRR = 0.82 (0.62–1.08)	
			Total fruits	Highest versus lowest category of intake (≥2 servings/day versus <2 servings/week)	IRR = 1.00 (0.74–1.35)	
			Post-menopausal women			
			Total fruits and vegetables	Highest versus lowest category of intake (≥4 servings/day versus <1 serving/day)	IRR = 0.76 (0.56–1.04)	
			Total vegetables	Highest versus lowest category of intake (≥2 servings/day versus <4 servings/week)	IRR = 0.86 (0.65–1.14)	
			Total fruits	Highest versus lowest category of intake (≥2 servings/day versus <2 servings/week)	IRR = 0.86 (0.63–1.18)	
			ER^+/PR^+ cases			
			Total fruits and vegetables	Highest versus lowest category of intake (≥4 servings/day versus <1 serving/day)	IRR = 0.96 (0.64–1.46)	
			Total vegetables	Highest versus lowest category of intake (≥2 servings/day versus <4 servings/week)	IRR = 1.41 (0.97–2.04)	
			Total fruits	Highest versus lowest category of intake (≥2 servings/day versus <2 servings/week)	IRR = 1.02 (0.69–1.50)	
			ER^+/PR^- cases			
			Total fruits and vegetables	Highest versus lowest category of intake (≥4 servings/day versus <1 serving/day)	IRR = 1.43 (0.69–2.94)	
			Total vegetables	Highest versus lowest category of intake (≥2 servings/day versus <4 servings/week)	IRR = 1.20 (0.61–2.36)	
			Total fruits	Highest versus lowest category of	IRR = 0.87 (0.73–1.05)	

				intake (≥2 servings/day versus <2 servings/week)		
			ER⁻/PR⁻ cases			
			Total fruits and vegetables	Highest versus lowest category of intake (≥4 servings/day versus <1 serving/day)	IRR = 0.84 (0.40–1.76)	
			Total vegetables	Highest versus lowest category of intake (≥2 servings/day versus <4 servings/week)	IRR = 0.57 (0.38–0.85)	
			Total fruits	Highest versus lowest category of intake (≥2 servings/day versus <2 servings/week)	IRR = 1.04 (0.67–1.61)	
Masala et al. (2012)	Cohort	32 578/1072 11.25 years	*Overall and specific sub-groups*			Weight, height, education, number of children, age at menarche, menopausal status, energy intake except alcohol, alcohol intake, current use of hormone therapy, smoking status, physical activity.
			Vegetables (all types)	Highest versus lowest quintile (>264.8 g/day versus <107.8 g/day)	HR = 0.65 (0.53–0.81)	
			Fruit (all types)	Highest versus lowest quintile (>476.8 g/day versus <195.3 g/day)	HR = 0.86 (0.70–1.05)	

(Felton et al., 2002; Snyderwine 2002; Snyderwine et al., 2002). Moreover, red meat contains heme iron, a major source of stored body iron. In humans, elevated body iron storage has been shown to increase the risk of several cancers including breast cancer (Kallianpur et al., 2008; Liehr & Jones 2001). Finally, a hypothesis includes the promotion of carcinogenesis by high fat intake, since meat and in particular, processed meat can be a rich source of saturated fat. Fat intake in general has been hypothesized to raise estrogen and androgen levels in plasma, through the promotion of intestinal re-absorption of estrogens by enhancement of de-conjugating enzyme activity (Forman, 2007), as well as to increase the risk of overweight and obesity, a risk factor for several different cancer sites, including breast cancer (WCRF/AICR, 2007).

In the light of the above results, further studies are necessary to describe the association between meat intake and the development of breast cancer even defined by ER and PR status, while taking into account factors such as meat processing and cooking in high temperatures.

Soy products and isoflavones

Soy products are rich in phytoestrogens, naturally occurring hormone-like compounds that can be subdivided into coumestans, lignans and the most known isoflavones. Several possible mechanisms have been identified for the anticarcinogenic activity of soy isoflavones. First, they are believed to decrease lipid peroxidation and oxidative DNA damage due to their antioxidant properties (Messina et al., 2006; Omoni & Aluko, 2005; Setchell, 1998). Secondly, due to the fact that their chemical structure is similar to that of estrogens, they are able to bind to the estrogen receptor and compete with estrogens (Adlercreutz & Mazur, 1998; Murkies et al., 1998; Omoni & Aluko, 2005). In fact, they are able to increase sex hormone binding globulin and inhibit important steroid biosynthetic enzymes, decreasing in these ways blood levels of estrogens and free estrogens (Adlercreutz & Mazur, 1997; Omoni & Aluko, 2005). Finally, other possible mechanisms by which isoflavones seem to be related to breast cancer risk are the induction of apoptosis (Messina et al., 2006) as well as the inhibition of angiogenesis (Fotsis et al., 1998; Setchell, 1998).

In this review, 24 studies comprising of 14 case–controls and 10 cohorts were included (Table 4). Two case–control studies (Do et al., 2007; Shannon et al., 2005) along with six cohort studies (Hedelin et al., 2008; Horn-Ross et al., 2002; Keinan-Boker et al., 2004; Touillaud et al., 2006; Travis et al., 2008; Ward et al., 2008) found no association between the intake of soy products, isoflavones and breast cancer risk. In contrast, the majority of the case–control studies demonstrated an inverse association between soy food/soy products, isoflavones and breast cancer risk (Dos Santoa Silva et al., 2004; Hirose et al., 2005; Iwasaki et al., 2008, 2009; Kim et al., 2008; Korde et al., 2009; Linseisen et al., 2004; Verheus et al., 2007; Wu et al., 2002; Zhang et al., 2009a,d; Zhu et al., 2011). It is important to highlight that only two of these studies were conducted in Western populations (Linseisen et al., 2004; Verheus et al., 2007), where the mean intake of isoflavones is substantially lower than in Asian countries.

In agreement with the results of the majority of case–control studies, in the Japan Public Health Center-Based Prospective Study on Cancer and Cardiovascular Diseases (JPHC Study) which included 21 852 Japanese female residents (aged 40–59 years) Yamamoto et al. (2003) concluded that isoflavone consumption was associated with a reduced risk of breast cancer. More recently, Goodman et al. (2009) conducted a nested-case–control study within the Multiethnic Cohort Study which included

Table 3. Studies on meat intake and breast cancer risk from 2002.

References	Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/ Type of meat	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
Holmes et al. (2003)	Cohort	88 647/4107 18 years	*All women*			Age, 2 year time period; total energy intake; alcohol intake; parity and age at first birth categories; Body mass index at age 18 in kg/m^2; weight change since age 18 in kg; height in inches; family history of breast cancer; history of benign breast disease; age at menarche in years; menopausal status, age at menopause and hormone replacement therapy (HRT) use categories; duration of menopause.
			All processed meat	Highest versus lowest quintile (≥0.46 servings/day versus ≤0.10 servings/day)	RR = 0.94 (0.85–1.05)	
			Red meat	Highest versus lowest quintile (≥1.32 servings/day versus ≤0.55 servings/day)	RR = 0.94 (0.84–1.05)	
			All meat	Highest versus lowest quintile (≥2.00 servings/day versus ≤1.11 servings/day)	RR = 0.89 (0.79–1.00)	
			Pre-menopausal			
			All processed meat	Highest versus lowest quintile (≥0.46 servings/day versus ≤0.10 servings/day)	RR = 0.86 (0.67–1.09)	
			Red meat	Highest versus lowest quintile (≥1.32 servings/day versus ≤0.55 servings/day)	RR = 0.94 (0.72–1.22)	
			All meat	Highest versus lowest quintile (≥2.00 servings/day versus ≤1.11 servings/day)	RR = 0.99 (0.86–1.13)	
			Post-menopausal			
			All processed meat	Highest versus lowest quintile (≥0.46 servings/day versus ≤0.10 servings/day)	RR = 1.00 (0.88–1.13)	
			Red meat	Highest versus lowest quintile (≥1.32 servings/day versus ≤0.55 servings/day)	RR = 0.99 (0.86–1.13)	
			All meat	Highest versus lowest quintile (≥2.00 servings/day versus ≤1.11 servings/day)	RR = 0.88 (0.77–1.02)	
Cho et al. (2006)	Cohort	90 659/1021 12 years	*Total breast cancer*			Smoking, height, parity and age at first birth, body mass index, age at menarche, family history of breast cancer, history of benign breast disease, oral contraceptive use, alcohol intake, and energy intake.
			Red meat	Highest versus lowest category of intake (>1.5 serving/day versus ≤3 servings/week)	RR = 1.27 (0.96–1.67)	
			ER^+/PR^+			
			Red meat	Highest versus lowest category of intake (>1.5 serving/day versus ≤3 servings/week)	RR = 1.97 (1.35–2.88)	
			ER^-/PR^-			
			Red meat	Highest versus lowest category of intake (>1.5 serving/day versus ≤3 servings/week)	RR = 0.89 (0.43–1.84)	
Taylor et al. (2007)	Cohort	35 372/1750 8 years	*All women*			Age, energy intake, BMI, physical activity, smoking status, HRT use, OCP use, parity, total fruit and vegetable intake.
			Total meat	Highest versus lowest category of intake (>103 g/day versus none)	HR = 1.34 (1.05–1.71)	
			Non-processed meat	Highest versus lowest category of intake (>84 g/day versus none)	HR = 1.33 (1.04–1.69)	

			Processed meat	Highest versus lowest category of intake (>20 g/day versus none)	HR = 1.39 (1.09–1.78)	
			Red meat	Highest versus lowest category of intake (>57 g/day versus none)	HR = 1.41 (1.11–1.81)	
			Pre-menopausal			
			Total meat	Highest versus lowest category of intake (>103 g/day versus none)	HR = 1.12 (1.02–1.23)	
			Non-processed meat	Highest versus lowest category of intake (>84 g/day versus none)	HR = 1.13 (1.01–1.26)	
			Processed meat	Highest versus lowest category of intake (>20 g/day versus none)	HR = 1.45 (0.95–2.23)	
			Red meat	Highest versus lowest category of intake (>57 g/day versus none)	HR = 1.13 (0.99–1.29)	
			Post-menopausal			
			Total meat	Highest versus lowest category of intake (>103 g/day versus none)	HR = 1.10 (1.01–1.20)	
			Non-processed meat	Highest versus lowest category of intake (>84 g/day versus none)	HR = 1.09 (0.99–1.20)	
			Processed meat	Highest versus lowest category of intake (>20 g/day versus none)	HR = 1.64 (1.19–2.27)	
			Red meat	Highest versus lowest category of intake (>57 g/day versus none)	HR = 1.12 (1.01–1.26)	
Egeberg et al. (2008)	Nested case–control	24 697/378 (378 controls)	Total meat	Highest versus lowest category of intake (>180 g/day versus <115 g/day)	IRR = 2.24 (1.43–3.49)	Parity, age at first birth, education, duration of hormone replacement therapy use, intake of alcohol and body mass index.
			Red meat	Highest versus lowest category of intake (>80 g/day versus <50 g/day)	IRR = 1.65 (1.09–2.50)	
			Processed meat	Highest versus lowest category of intake (>45 g/day versus <20 g/day)	IRR = 1.59 (1.02–2.47)	
Sonestedt et al. (2008)	Cohort	11 699/430 mean 10.4 years	Heterocyclic Amines (Has)	Highest versus lowest quintile of median intake (978 ng/day versus 201 ng/day)	HR = 0.95 (0.69–1.29)	Age, method, season, total energy intake, weight, height, smoking habits, alcohol consumption, leisure time physical activity, hours of household work, educational level, current use of hormone replacement therapy, age at menopause.
Lima et al. (2008)	Case–control	89/94	Red meat	Highest versus lowest category of intake (≥7 portions/week versus <7 portions/week)	OR = 4.30 (1.74–10.67)	Age group, origin, oral contraceptives, age at menopause, body mass index, and energy.
			Fried meat	Highest versus lowest category of intake (>7 portions/week versus ≤2.8 portions/week)	OR = 4.69 (1.29–17.06)	
Aune et al. (2009b)	Case–control	3539/2032	Total meat	Highest versus lowest category of intake (250–686.8 g/day versus 0 to <150 g/day)	OR = 2.05 (1.23–3.42)	Age, sex, residence, education, income, interviewer, smoking status, cigarettes per day, duration of smoking, age at starting, years since quitting, alcohol, dairy foods, grains, fatty foods, fruits and
			Red meat	Highest versus lowest category of intake (250–600 g/day versus 0 to <150 g/day)	OR = 1.97 (1.04–3.75)	

(*continued*)

Table 3. Continued

References	Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/ Type of meat	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
			Processed meat	Highest versus lowest category of intake (>40 to 258.8 g/day versus 0–10 g/day)	OR = 1.53 (1.01–2.30)	vegetables, fish, poultry, mate drinking, BMI and energy intake. Red meat was adjusted for processed meat and vice versa.
Ferrucci et al. (2009)	Multicenter RCT	52 158/1205 mean 5.5 years	Red meat	Highest versus lowest quintile (>42.5 to 196.3 g/1000 kcal versus ≤14.6 g/1000 kcal)	HR = 1.23 (1.00–1.51)	Age, race, education, study centre, randomization group, family history of breast cancer, age at menarche, age at menopause, age at first birth and number of live births, history of benign breast disease, number of mammograms during past 3 years, menopausal hormone therapy use, body mass index, alcohol intake, total fat intake, and total energy intake.
			Processed meat	Highest versus lowest quintile (>11.6 to 124.1 g/1000 kcal versus ≤2.4 g/1000 kcal)	HR = 1.12 (0.92–1.36)	
			MelQx	Highest versus lowest quintile (>18.2 to 516.2 ng/day versus ≤2.8 ng/day)	HR = 1.26 (1.03–1.55)	
			DiMelQx	Highest versus lowest quintile (>1.6–76.2 ng/day versus ≤0.1 ng/day)	HR = 1.18 (0.98–1.42)	
Kabat et al. (2009)	Cohort	120 755/3818 8 years	Total meat	Highest versus lowest quintile (>89.1 g/1000 kcal versus ≤38.2 g/1000 kcal)	HR = 1.03 (0.93–1.15)	Age at entry, body mass index, age at first menstrual period, age at first live birth, family history of breast cancer, hormone replacement therapy, education, race, total energy intake, gm saturated fat, alcohol intake, physical activity, smoking, age at menopause, number of breast biopsies, height.
			Red meat	Highest versus lowest quintile (>43.7 g/1000 kcal versus ≤13.0 g/1000 kcal)	HR = 1.05 (0.93–1.18)	
			White meat	Highest versus lowest quintile (>52.2 g/1000 kcal versus ≤14.9 g/1000 kcal)	HR = 0.93 (0.84–1.04)	
			Processed meat	Highest versus lowest quintile (>12.5 g/1000 kcal versus ≤2.2 g/1000 kcal)	HR = 1.00 (0.90–1.12)	
			Meat cooked at high temperatures	Highest versus lowest quintile (>18.0 g/1000 kcal versus ≤3.5 g/1000 kcal)	HR = 0.98 (0.86–1.11)	
Larsson et al. (2009b)	Cohort	61 433/2952 mean 17.4 years	*Total red meat*			Stratified by age in months at the start of each follow–up period and calendar year of the questionnaire cycle. Education, body mass index, height, parity and age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of post-menopausal hormones, family history of breast cancer, intakes of total energy and alcohol.
			Total breast cancer	Highest versus lowest quintile (≥98 g/day versus <46 g/day)	RR = 0.98 (0.86–1.12)	
			ER^+/PR^+ tumors	Highest versus lowest quintile (≥98 g/day versus <46 g/day)	RR = 1.10 (0.90–1.34)	
			ER^+/PR^- tumors	Highest versus lowest quintile (≥98 g/day versus <46 g/day)	RR = 0.86 (0.60–1.23)	
			ER^-/PR^- tumors	Highest versus lowest quintile (≥98 g/day versus <46 g/day)	RR = 1.12 (0.70–1.79)	
			Pan-fried meat			
			Total breast cancer	Highest versus lowest quintile (≥10 times/month versus <4 times/month)	RR = 1.10 (0.93–1.30)	
			ER^+/PR^- tumors	Highest versus lowest quintile (≥10 times/month versus <4 times/month)	RR = 1.45 (1.03–2.03)	

Mignone et al. (2009)	Case–control	2686/3508	*All women*			Age, state of residence, body mass index, education, alcohol intake, age at menarche, menopausal status (only in analysis of all women), age at first birth, family history of breast cancer, history of benign breast disease, parity, postmenopausal hormone use, multivitamin use, total fruits and vegetables intake, and smoking (smoking status and pack years).
			Total meat	Highest versus lowest category of intake (5 or more servings/week versus <2 servings/week)	OR = 0.99 (0.84–1.15)	
			Red meat	Highest versus lowest category of intake (5 or more servings/week versus <2 servings/week)	OR = 0.88 (0.65–1.21)	
			Chicken	Highest versus lowest quintile	OR = 1.04 (0.84–1.29)	
			PhIP	Highest versus lowest quintile	OR = 1.01 (0.85–1.18)	
			DiMelQx	Highest versus lowest quintile	OR = 1.06 (0.89–1.25)	
			MelQx	Highest versus lowest quintile	OR = 1.01 (0.85–1.19)	
			Total mutagenic activity	Highest versus lowest category of intake (5 or more servings/week versus <2 servings/week)	OR = 0.74 (0.57–0.95)	
			Pre-menopausal			
			Total meat	Highest versus lowest category of intake (5 or more servings/week versus <2 servings/week)	OR = 0.82 (0.60–1.13)	
			Red meat	Highest versus lowest category of intake (4 or more servings/week versus <1 servings/week)	OR = 0.67 (0.42–1.08)	
			Chicken	Highest versus lowest quintile	OR = 0.87 (0.63–1.09)	
			PhIP	Highest versus lowest quintile	OR = 0.85 (0.66–1.11)	
			DiMelQx	Highest versus lowest quintile	OR = 1.04 (0.79–1.37)	
			MelQx	Highest versus lowest quintile	OR = 0.88 (0.67–1.16)	
			Total mutagenic activity	Highest versus lowest category of intake (5 or more servings/week versus <2 servings/week)	OR = 1.19 (0.97–1.46)	
			Post-menopausal			
			Total meat	Highest versus lowest category of intake (5 or more servings/week versus <2 servings/week)	OR = 1.02 (0.80–1.31)	
			Red meat	Highest versus lowest category of intake (5 or more servings/week versus <2 servings/week)	OR = 1.02 (0.80–1.31)	
			Chicken	Highest versus lowest category of intake (4 or more servings/week versus <1 servings/week)	OR = 1.11 (0.72–1.71)	
			PhIP	Highest versus lowest quintile	OR = 1.21 (0.97–1.52)	
			DiMelQx	Highest versus lowest quintile	OR = 1.18 (0.95–1.48)	
			MelQx	Highest versus lowest quintile	OR = 1.11 (0.90–1.40)	
			Total mutagenic activity	Highest versus lowest quintile	OR = 1.17 (0.93–1.46)	
Pala et al. (2009)	Cohort	319 826/7119 median 8.8 years	*All cases*			Energy, height, weight, years of schooling, alcohol intake, smoking and menopause (only in analysis for all cases); stratified by center and age (1-year strata).
			Red meat	Highest versus lowest quintile (84.6 g/day versus 1.4 g/day)	HR = 1.06 (0.98–1.14)	
			Poultry	Highest versus lowest quintile (46.1 g/day versus 0 g/day)	HR = 1.02 (0.95–1.11)	
			Processed meat	Highest versus lowest quintile (56.5 g/day versus 1.7 g/day)	HR = 1.10 (1.00–1.20)	

(*continued*)

Table 3. Continued

References	Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/ Type of meat	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
			Pre-menopausal			
			Red meat	Highest versus lowest quintile (84.6 g/day versus 1.4 g/day)	HR = 0.94 (0.80–1.10)	
			Poultry	Highest versus lowest quintile (46.1 g/day versus 0 g/day)	HR = 0.98 (0.83–1.16)	
			Processed meat	Highest versus lowest quintile (56.5 g/day versus 1.7 g/day)	HR = 0.99 (0.82–1.19)	
			Post-menopausal			
			Red meat	Highest versus lowest quintile (84.6 g/day versus 1.4 g/day)	HR = 1.05 (0.94–1.18)	
			Poultry	Highest versus lowest quintile (46.1 g/day versus 0 g/day)	HR = 1.05 (0.94–1.17)	
			Processed meat	Highest versus lowest quintile (56.5 g/day versus 1.7 g/day)	HR = 1.13 (1.00–1.28)	
Zhang et al. (2009c)	Case–control	438/438	Total meat	Highest versus lowest quartile	OR = 1.00 (0.63–1.58)	Age at menarche, live birth and age at first live birth, BMI, history of benign breast disease, mother/ sister/daughter with breast cancer, physical activity, passive smoking, use of deep-fried cooking method, total energy, vegetable, fruit, and soy food intake.
			Red meat	Highest versus lowest quartile	OR = 1.32 (0.84–2.09)	
			Organ meat	Highest versus lowest quartile	OR = 1.16 (0.79–1.71)	
			Processed meat	Highest versus lowest quartile	OR = 1.44 (0.97–2.15)	
			Poultry	Highest versus lowest quartile	OR = 0.82 (0.53–1.27)	
Fu et al. (2011)	Case–control	2386/1703	*Pre-menopausal women*			Age group, ethnicity, educational attainment, family income, total energy intake, first degree relative breast cancer history, personal history of benign breast disease, hormone replacement therapy, age at menarche, have live birth, BMI, regular physical exercise, regular alcohol consumption, and study period.
			Total meat	Highest versus lowest quartile	OR = 1.30 (0.90–1.80)	
			Red meat	Highest versus lowest quartile	OR = 1.30 (0.90–2.00)	
			Well-done red meat	Highest versus lowest quartile	OR = 1.50 (1.10–2.20)	
			MelQx	Highest versus lowest quartile	OR = 0.80 (0.50–1.10)	
			DiMelQx	Highest versus lowest quartile	OR = 0.90 (0.70–1.30)	
			Post-menopausal women			
			Total meat	Highest versus lowest quartile	OR = 0.90 (0.70–1.30)	
			Red meat	Highest versus lowest quartile	OR = 1.70 (1.30–2.40)	
			Well-done red meat	Highest versus lowest quartile	OR = 1.70 (1.20–2.30)	
			MelQx	Highest versus lowest quartile	OR = 1.40 (1.10–1.90)	
			DiMelQx	Highest versus lowest quartile	OR = 1.40 (1.10–1.80)	

Table 4. Studies on soy products and isoflavones intake and breast cancer risk from 2002.

References	Country or region/ Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/items	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
Wu et al. (2002)	USA/Case–control	501/594	Tofu intake during adolescence	Highest category of intake versus lowest category of intake (4 or more times/ week versus less than monthly)	OR = 0.65 (0.38–1.10)	Age, ethnicity, birthplace, education, age at menarche, pregnancy, current BMI, menopausal status, use of menopausal hormones, intake of dark leafy greens during adolescence, smoking history, alcohol intake, physical activity and family history of breast cancer.
			Adult intake of isoflavone	Highest category of intake versus lowest category of intake(>12.68 mg/1000 kcal versus ≤1.79 mg/1000 kcal)	OR = 0.61 (0.39–0.97)	
			Both adolescent tofu and adult isoflavone intake	Highest category of intake versus lowest category of intake (weekly or more versus monthly or less)	OR = 0.65 (0.43–0.97)	
Yamamoto et al. (2003)	Japan/Cohort	21 852/179 209 354 person-years	Miso soup	Highest versus lowest quartile (≥3 cups/day versus <1 cup/day)	RR = 0.60 (0.34–1.10)	Area, age, age at menarche, number of pregnancies, menopausal status, age at first pregnancy, active and passive smoking, alcohol consumption, leisure-time physical activity, educational level, total energy and meat, fish, vegetable, and fruit consumption.
			Soyfoods	Highest versus lowest quartile (almost daily versus <2 times/week)	RR = 0.81 (0.49–1.30)	
			Isoflavone	Highest versus lowest quartile (highest versus lowest)	RR = 0.46 (0.25–0.84)	
Keinan-Boker et al. (2004)	Germany/Cohort	15 555/280 median 5.2 years	Isoflavones	Highest versus lowest quartile (1.36–79.08 mg/day versus 0.10–0.84 mg/day)	HR = 0.98 (0.65–1.48)	Age at enrollment, age at first full-term delivery, height, weight, parity, physical activity score, use of oral contraceptives or hormone replacement therapy, marital status, academic education, and daily energy intake.
			Lignans	Highest versus lowest quartile (1.36–79.08 mg/day versus 0.10–0.84 mg/day)	HR = 0.70 (0.46–1.09)	
Linseisen et al. (2004)	German/Case–control	278/666	Genistein	Highest versus lowest quartile	OR = 0.47 (0.29–0.74)	First-degree family history of breast cancer, number of births, duration of breast-feeding, energy intake, BMI, alcohol consumption and education.
			Daidzein + genistein	Highest versus lowest quartile	OR = 0.56 (0.36–0.87)	
			Matairesinol	Highest versus lowest quartile	OR = 0.58 (0.37–0.94)	
			Enterodiol	Highest versus lowest quartile	OR = 0.61 (0.39–0.98)	
			Enterolactone	Highest versus lowest quartile	OR = 0.57 (0.35–0.92)	
			Intestinal lignan metabolites	Highest versus lowest quartile	OR = 0.61 (0.39–0.98)	
Shannon et al. (2005)	China/Case–control	378/1070	Total soyfood	Highest versus lowest category of intake (≥1.1 servings/day versus ≤2.6 servings/week)	OR = 1.07 (0.68–1.69)	Age, total energy intake, and breast-feeding.
Hirose et al. (2005)	Japan/Case–control	167/854	*Pre-menopausal women*			Age, motives for consultation, smoking, drinking, exercise, energy, family history, age at menarche, parity, age at first full-term pregnancy, BMI and age at menopause for postmenopausal women.
			Soybean products	Highest versus lowest tertile (54.4 mg/ 1000 kcal versus 24.3 mg/1000 kcal)	OR = 0.53 (0.27–1.04)	
			Tofu	Highest versus lowest tertile (31.3 mg/ 1000 kcal versus 8.9 mg/1000 kcal)	OR = 0.49 (0.25–0.95)	
			Isoflavones	Highest versus lowest tertile (18.47 mg/ 1000 kcal versus 7.61 mg/1000 kcal)	OR = 0.44 (0.22–0.89)	

(*continued*)

Table 4. Continued

References	Country or region/ Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/items	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
			Post-menopausal women			
			Soybean products	Highest versus lowest tertile (54.4 mg/ 1000 kcal versus 24.3 mg/1000 kcal)	OR = 0.70 (0.37–1.33)	
			Tofu	Highest versus lowest tertile (31.3 mg/ 1000 kcal versus 8.9 mg/1000 kcal)	OR = 0.71 (0.36–1.39)	
			Isoflavones	Highest versus lowest tertile (18.47 mg/ 1000 kcal versus 7.61 mg/1000 kcal)	OR = 0.58 (0.30–1.10)	
Touillaud et al. (2006)	France/Cohort	26 868/402 median4.2 years	Total isoflavones	Highest versus lowest quartile (36–112 μg/day versus 1–22 μg/day)	RR = 1.00 (0.76–1.31)	Years of education, height, body mass index category, age at menarche, personal history of benign breast disease or lobular carcinoma in situ, family history of breast cancer in first- or second-degree relatives, lifetime use of oral contraceptive, age at first full-term pregnancy (FFTP) and parity, geographic area, alcohol consumption and dietary energy intake from food.
			Coumestrol	Highest versus lowest quartile (0.06–0.60 μg/day versus 0 μg/day)	OR = 1.22 (0.89–1.66)	
			Total plant lignans	Highest versus lowest quartile (1357–4611 μg/day versus 41–843 μg/day)	OR = 1.07 (0.81–1.41)	
			Total enterolignans	Highest versus lowest quartile (1289–3361 μg/day versus 168–902 μg/day)	OR = 0.94 (0.71–1.24)	
Do et al. (2007)	Case–control/Korea	359/708	Total soyfoods	Highest versus lowest quartile (>28.81 g/day versus <6.82 g/day)	OR = 0.70 (0.37–1.19)	Age, education, income, age at menarche, parity, age at first live birth, history of breastfeeding, use of hormones (oral contraceptives and hormone replacement), family history of breast cancer in a first-degree relative, frequency of exercise, physical activity, cigarette smoking, and alcohol consumption.
			Soybeans	Highest versus lowest quartile (>3.03 g/day versus <0.31 g/day)	OR = 0.67 (0.45–0.91)	
			Soybean curd	Highest versus lowest quartile (>14.39 g/day versus <5.10 g/day)	OR = 0.71 (0.41–1.15)	
			Soymilk	Highest versus lowest quartile (>3.12 g/day versus <0.31 g/day)	OR = 0.76 (0.56–1.33)	
			Soybean paste	Highest versus lowest quartile (>9.24 g/day versus <1.82 g/day)	OR = 0.71 (0.54–1.30)	
Verheus et al. (2007)	Germany/Nested case–control	383/383	*All cases*			Age at menarche (for daidzein and genistein). Age at menarche, ever OC use, parity, and age at first childbirth (for O-DMA). Age at menarche and having a family history of breast cancer (for enterolactone). Crude ORs for glycitein, equol and enterodiol.
			Daidzein	Highest versus lowest tertile	OR = 0.83 (0.58–1.19)	
			Genistein	Highest versus lowest tertile	OR = 0.68 (0.47–0.98)	
			Glycitein	Highest versus lowest tertile	OR = 0.83 (0.59–1.18)	
			O-DMA	Highest versus lowest tertile	OR = 0.83 (0.59–1.18)	
			Equol	Highest versus lowest tertile	Not reported	
			Enterodiol	Highest versus lowest tertile	OR = 1.07 (0.75–1.53)	
			Enterolactone	Highest versus lowest tertile	OR = 1.10 (0.76–1.57)	
			Pre- or Peri-menopausal women			
			Daidzein	Highest versus lowest tertile	OR = 0.80 (0.34–1.88)	
			Genistein	Highest versus lowest tertile	OR = 0.80 (0.38–1.69)	
			Glycitein	Highest versus lowest tertile	OR = 0.92 (0.42–2.03)	
			O-DMA	Highest versus lowest tertile	OR = 0.66 (0.26–1.65)	
			Equol	Highest versus lowest tertile	Not reported	
			Enterodiol	Highest versus lowest tertile	OR = 1.45 (0.69–3.05)	
			Enterolactone	Highest versus lowest tertile	OR = 1.72 (0.80–3.71)	
			Post-menopausal women			

			Daidzein	Highest versus lowest tertile	OR = 0.88 (0.59–1.32)	
			Genistein	Highest versus lowest tertile	OR = 0.69 (0.45–1.04)	
			Glycitein	Highest versus lowest tertile	OR = 0.81 (0.53–1.24)	
			O-DMA	Highest versus lowest tertile	OR = 0.82 (0.55–1.23)	
			Equol	Highest versus lowest tertile	Not reported	
			Enterodiol	Highest versus lowest tertile	OR = 0.91 (0.60–1.39)	
			Enterolactone	Highest versus lowest tertile	OR = 0.97 (0.63–1.48)	
Hedelin et al. (2008)	Sweden/Cohort	45 448/1014	*All women*			Age, BMI, oral contraceptives, age at first pregnancy, age at menarche, parity, cancer in sisters or mothers, and intake of total energy intake, alcohol and saturated fat.
			Total lignans	Highest versus lowest quartile	RR = 1.09 (0.91–1.31)	
			Total isoflavonoids	Highest versus lowest quartile	RR = 0.98 (0.83–1.17)	
			Women < 50 years			
			Total lignans	Highest versus lowest quartile	RR = 1.11 (0.86–1.45)	
			Total isoflavonoids	Highest versus lowest quartile	RR = 1.04 (0.81–1.34)	
			Women ≥ 50 years			
			Total lignans	Highest versus lowest quartile	RR = 1.07 (0.83–1.38)	
			Total isoflavonoids	Highest versus lowest quartile	RR = 0.93 (0.73–1.18)	
Travis et al. (2008)	Great Britain/Cohort	37 643/585 7.4 years	*Isoflavone intake*			Height, body mass index group, age at menarche, age at first birth and parity, alcohol consumption, and daily energy intake, and where appropriate, menopausal status and current HRT use.
			All women	Highest versus lowest category intake (20 or more mg/day versus <10 mg/day)	HR = 1.17 (0.79–1.71)	
			Pre-menopausal	Highest versus lowest category intake (10 or more mg/day versus <10 mg/day)	HR = 1.31 (0.95–1.81)	
			Post-menopausal	Highest versus lowest category intake (10 or more mg/day versus <10 mg/day)	HR = 0.95 (0.66–1.38)	
			Non-HRT users	Highest versus lowest category intake (10 or more mg/day versus <10 mg/day)	HR = 1.16 (0.92–1.48)	
Ward et al. (2008)	Great Britain/Case–control	237/952	*Full study*			Log2-transformed and adjusted for weight, oral contraceptive use, menopausal hormone treatment, menopausal status, parity, menarche, breastfeeding, family history of breast cancer, daily intake of fat and energy, and batch.
			Total serum isoflavones	Not reported	OR = 1.03 (0.95–1.11)	
			Total serum lignans			
			Total urinary isoflavones	Not reported	OR = 0.99 (0.90–1.08)	
			Total urinary lignans	Not reported	OR = 1.08 (1.00–1.16)	
			ER^+ *subgroup*	Not reported	OR = 1.01 (0.94–1.09)	
			Total serum isoflavones	Not reported	OR = 1.01 (0.91–1.12)	
			Total serum lignans	Not reported	OR = 1.02 (0.89–1.17)	
			Total urinary isoflavones	Not reported	OR = 1.09 (0.97–1.22)	
			Total urinary lignans	Not reported	OR = 1.12 (0.99–1.28)	
Iwasaki et al. (2008)	Japan/Nested case–control	24 226/144(288)	Plasma genistein	Highest versus lowest quartile	OR = 0.34 (0.16–0.74)	Number of births and age at first birth.
			Plasma daidzein	Highest versus lowest quartile	OR = 0.71 (0.35–1.44)	
			Dietary genistein intake	Highest versus lowest quartile	OR = 0.58 (0.29–1.18)	
			Dietary daidzein intake	Highest versus lowest quartile	OR = 0.67 (0.33–1.39)	
Kim et al. (2008)	Korea/Case–control	362/362	*All cases*			Drinking, multivitamin use, number of children, breast feeding, quintile of carbohydrate intake, quintiles of energy, vitamin E, and folate.
			Soy protein intake	Highest versus lowest quintile (≥10.55 g/day versus <4.24 g/day)	OR = 0.46 (0.26–0.83)	
			Total tofu intake	Highest versus lowest quintile (≥49.50 g/day versus <7.73 g/day)	OR = 0.31 (0.17–0.57)	
			Tofu as the main ingredient	Highest versus lowest quintile (>1 slice/day versus none)	OR = 0.36 (0.20–0.65)	
			Pre-menopausal women			

(*continued*)

Table 4. Continued

References	Country or region/ Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/items	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
			Soy protein intake	Highest versus lowest quintile (≥10.55 g/day versus <4.24 g/day)	OR = 0.39 (0.22–0.93)	
			Total tofu intake	Highest versus lowest quintile (≥49.50 g/day versus <7.73 g/day)	OR = 0.23 (0.11–0.48)	
			Tofu as the main ingredient	Highest versus lowest quintile (>1 slice/ day versus none)	OR = 0.26 (0.13–0.55)	
			Post-menopausal women			
			Soy protein intake	Highest versus lowest quintile (≥10.55 g/day versus <4.24 g/day)	OR = 0.22 (0.06–0.88)	
			Total tofu intake	Highest versus lowest quintile (≥49.50 g/day versus <7.73 g/day)	OR = 0.39 (0.11–1.90)	
			Tofu as the main ingredient	Highest versus lowest quintile (>1 slice/ day versus none)	OR = 0.62 (0.19–2.00)	
Wu et al. (2008)	China/Cohort	34 028/629 338 242 person years	*Soy isoflavone intake*			Age, years of interview, dialect, education, family history of breast cancer, parity, age when period became regular, menopausal status (if applicable), body mass index, and n-3 fatty acid.
			All subjects	Highest versus lowest category of intake (≥10.6 mg/1000 kcal versus <10.6 mg/1000 kcal)	RR = 0.82 (0.70–0.97)	
			Pre-menopausal	Highest versus lowest category of intake (≥10.6 mg/1000 kcal versus <10.6 mg/1000 kcal)	RR = 1.04 (0.77–1.40)	
			Post-menopausal	Highest versus lowest category of intake (≥10.6 mg/1000 kcal versus <10.6 mg/1000 kcal)	RR = 0.74 (0.61–0.90)	
			ER^+	Highest versus lowest category of intake (≥10.6 mg/1000 kcal versus <10.6 mg/1000 kcal)	RR = 0.67 (0.49–0.91)	
			PR^+	Highest versus lowest category of intake (≥10.6 mg/1000 kcal versus <10.6 mg/1000 kcal)	RR = 0.69 (0.48–1.00)	
			ER^+/PR^+	Highest versus lowest category of intake (≥10.6 mg/1000 kcal versus <10.6 mg/1000 kcal)	RR = 0.70 (0.48–1.01)	
			ER^-	Highest versus lowest category of intake (≥10.6 mg/1000 kcal versus <10.6 mg/1000 kcal)	RR = 0.66 (0.42–1.02)	
			PR^-	Highest versus lowest category of intake (≥10.6 mg/1000 kcal versus <10.6 mg/1000 kcal)	RR = 0.67 (0.47–0.95)	
			ER^-/PR^-	Highest versus lowest category of intake (≥10.6 mg/1000 kcal versus <10.6 mg/1000 kcal)	RR = 0.70 (0.45–1.10)	
			ER DK	Highest versus lowest category of intake (≥10.6 mg/1000 kcal versus <10.6 mg/1000 kcal)	RR = 0.89 (0.64–1.22)	

			PR DK	Highest versus lowest category of intake (≥10.6 mg/1000 kcal versus <10.6 mg/1000 kcal)	RR = 0.85 (0.62–1.17)	
			ER and PR DK	Highest versus lowest category of intake (≥10.6 mg/1000 kcal versus <10.6 mg/1000 kcal)	RR = 0.89 (0.64–1.22)	
Iwasaki et al. (2009)	Japan–Brazil/Case–control	850/850	*Dietary isoflavone intake*			Menopausal status, number of births, family history of breast cancer, smoking status, moderate physical activity in the past 5 years, and vitamin supplement use.
			Japanese Brazilians	Highest versus lowest tertile	OR = 0.25 (0.09–0.68)	
			Non-Japanese Brazilians	Highest versus lowest tertile	OR = 0.56 (0.35–0.90)	
			All subjects in three populations	Highest quintile category of consumers versus non-consumers (median isoflavone intake = 71.3 mg/day versus 0)	OR = 0.43 (0.24–0.76)	
Korde et al. (2009)	USA/Case–control	597/966	Childhood soy intake	Highest versus lowest tertile (1.5–8.8 times/week versus 0–0.75)	OR = 0.40 (0.18–0.86)	Age at diagnosis, ethnicity, study center, parity/age at first live birth, menopausal status at diagnosis, age at menarche, family history of breast cancer, and personal history of benign breast disease.
			Adolescence soy intake	Highest versus lowest tertile (2.0–8.9 times/week versus 0–0.50)	OR = 0.80 (0.59–1.08)	
			Adulthood soy intake	Highest versus lowest tertile (1.11–12.0 times/week versus 0–0.43)	OR = 0.76 (0.56–1.02)	
Lee et al. (2009)	Shanghai/Cohort	73 223/592 7.4 years	*Pre-menopausal women*			Age, education, physical activity, age at first live birth, BMI, season of recruitment, family history of breast cancer, total energy intake, and total fruit and vegetable intakes during adolescence (for associations during adolescence).
			Adult soy protein intake	Highest versus lowest quintile (≥12.84 g/day versus ≤4.87 g/day)	RR = 0.41 (0.25–0.70)	
			Adult isoflavones intake	Highest versus lowest quintile (≥44.24 mg/day versus ≤15.93 mg/day)	RR = 0.44 (0.26–0.73)	
			Pre-menopausal women			
			Adolescence soy protein intake	Highest versus lowest quintile (≥11.33 g/day versus ≤2.76 g/day)	RR = 0.57 (0.34–0.97)	
			Adolescence isoflavones intake	Highest versus lowest quintile (≥31.28 mg/day versus ≤7.34 mg/day)	RR = 0.89 (0.57–1.40)	
Goodman et al. (2009)	USA/Nested case–control	36 458/251(462)	*All subjects*			Age at blood draw and fasting hours prior to blood draw.
			Daidzein	Highest versus lowest quartile (2.536 or more nmol/mg creatinine versus 0–0.183 nmol/mg creatinine)	OR = 0.76 (0.47–1.21)	
			Genistein	Highest versus lowest quartile (0.647 or more nmol/mg creatinine versus 0–0.022 nmol/mg creatinine)	OR = 0.79 (0.49–1.28)	
			Equol	Highest versus lowest quartile (0.014 or more nmol/mg creatinine versus 0–0.001 nmol/mg creatinine)	OR = 0.99 (0.62–1.56)	
			Daidzein + Genistein	Highest versus lowest quartile (3.217 or more nmol/mg creatinine versus 0–0.218 nmol/mg creatinine)	OR = 0.70 (0.44–1.13)	
			Daidzein + Genistein + Equol	Highest versus lowest quartile (3.684 or more nmol/mg creatinine versus 0–0.229 nmol/mg creatinine)	OR = 0.69 (0.43–1.10)	
			Japanese–American			
			Daidzein	Highest versus lowest quartile (2.536 or more nmol/mg creatinine versus 0–0.183 nmol/mg creatinine)	OR = 0.41 (0.19–0.89)	
			Genistein	Highest versus lowest quartile (0.647 or more nmol/mg creatinine versus 0–0.022 nmol/mg creatinine)	OR = 0.62 (0.29–1.32)	

(*continued*)

Table 4. Continued

References	Country or region/ Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/items	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
			Equol	Highest versus lowest quartile (0.014 or more nmol/mg creatinine versus 0–0.001 nmol/mg creatinine)	OR = 1.32 (0.70–2.49)	
			Daidzein + Genistein	Highest versus lowest quartile (3.217 or more nmol/mg creatinine versus 0–0.218 nmol/mg creatinine)	OR = 0.51 (0.23–1.13)	
			Daidzein + Genistein + Equol	Highest versus lowest quartile (3.684 or more nmol/mg creatinine versus 0–0.229 nmol/mg creatinine)	OR = 0.53 (0.24–1.16)	
			White			
			Daidzein	Highest versus lowest quartile (2.536 or more nmol/mg creatinine versus 0–0.183 nmol/mg creatinine)	OR = 1.22 (0.46–3.22)	
			Genistein	Highest versus lowest quartile (0.647 or more nmol/mg creatinine versus 0–0.022 nmol/mg creatinine)	OR = 0.98 (0.35–2.73)	
			Equol	Highest versus lowest quartile (0.014 or more nmol/mg creatinine versus 0–0.001 nmol/mg creatinine)	OR = 0.27 (0.08–0.95)	
			Daidzein + Genistein	Highest versus lowest quartile (3.217 or more nmol/mg creatinine versus 0–0.218 nmol/mg creatinine)	OR = 0.97 (0.37–2.54)	
			Daidzein + Genistein + Equol	Highest versus lowest quartile (3.684 or more nmol/mg creatinine versus 0–0.229 nmol/mg creatinine)	OR = 0.85 (0.32–2.25)	
Zhang et al. (2009a)	China/Case–control	438/438	Soy isoflavone intake	Highest versus lowest quartile (>16.89 mg/day versus <3.26 mg/day)	OR = 0.54 (0.34–0.84)	Age at menarche, body mass index (BMI), history of benign breast disease, mother / sister / daughter with breast cancer, physical activity, passive smoking total energy, total vegetable, and total fruit intake.
			Soy protein intake	Highest versus lowest quartile (>4.66 g/day versus <0.93 g/day)	OR = 0.62 (0.40–0.96)	
			Soy isoflavone intake	Highest versus lowest quartile (>16.89 mg/day versus <3.26 mg/day)	OR = 0.54 (0.32–0.91)	
			ER^+	Highest versus lowest quartile (>16.89 mg/day versus <3.26 mg/day)	OR = 0.46 (0.23–0.92)	
			ER^-	Highest versus lowest quartile (>16.89 mg/day versus <3.26 mg/day)	OR = 0.52 (0.32–0.85)	
			PR^+	Highest versus lowest quartile (>16.89 mg/day versus <3.26 mg/day)	OR = 0.55 (0.32–0.92)	
			ER^+/PR^+	Highest versus lowest quartile (>16.89 mg/day versus <3.26 mg/day)	OR = 0.42 (0.18–0.96)	
			ER^-/PR^+	Highest versus lowest quartile (>16.89 mg/day versus	OR = 0.46 (0.26–0.82)	

			Pre-menopausal women	<3.26 mg/day)		
Zhang et al. (2009d)	China/Case–control	756/1009	*Total isoflavone intake – All women*			Age at interview, residential area, education, BMI, age at menarche, oral contraceptive use, hormone replacement therapy, breast cancer in first degree relatives, menopausal status, alcohol consumption, tobacco smoking, passive smoking, tea drinking, physical activity and total energy intake.
			ER^+	Highest versus lowest quartile (>25.40 mg/day versus <7.78 mg/day)	OR = 0.39 (0.27–0.58)	
			ER^-	Highest versus lowest quartile (>25.40 mg/day versus <7.78 mg/day)	OR = 0.32 (0.21–0.49)	
			PR^+	Highest versus lowest quartile (>25.40 mg/day versus <7.78 mg/day)	OR = 0.43 (0.29–0.64)	
			PR^-	Highest versus lowest quartile (>25.40 mg/day versus <7.78 mg/day)	OR = 0.30 (0.19–0.45)	
			Total isoflavone intake – Pre-menopausal women	Highest versus lowest quartile (>25.40 mg/day versus <7.78 mg/day)	OR = 0.44 (0.28–0.70)	
			ER^+	Highest versus lowest quartile (>25.40 mg/day versus <7.78 mg/day)	OR = 0.36 (0.21–0.62)	
			ER^-	Highest versus lowest quartile (>25.40 mg/day versus <7.78 mg/day)	OR = 0.50 (0.31–0.79)	
			PR^+	Highest versus lowest quartile (>25.40 mg/day versus <7.78 mg/day)	OR = 0.32 (0.19–0.55)	
			PR^-			
			Total isoflavone intake – Post-menopausal women			
			ER^+	Highest versus lowest quartile (>25.40 mg/day versus <7.78 mg/day)	OR = 0.31 (0.15–0.64)	
			ER^-	Highest versus lowest quartile (>25.40 mg/day versus <7.78 mg/day)	OR = 0.25 (0.11–0.54)	
			PR^+	Highest versus lowest quartile (>25.40 mg/day versus <7.78 mg/day)	OR = 0.32 (0.15–0.69)	
			PR^-	Highest versus lowest quartile (>25.40 mg/day versus <7.78 mg/day)	OR = 0.25 (0.12–0.51)	
Zhu et al. (2011)	China/Case–control	183/192	*Soy isoflavone intake*			Age, smoking, passive smoking, drinking, family history of cancer, history of breast disease, vegetables and fruit.
			Post- or peri-menopausal women	Highest versus lowest category of intake (>28.83 mg/day versus <7.56 mg/day)	OR = 0.57 (0.29–0.83)	
			ER^+/PR^+	Highest versus lowest category of intake (>28.83 mg/day versus	OR = 0.47 (0.19–0.85)	

(*continued*)

Table 4. Continued

References	Country or region/ Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/items	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
			Soy protein intake	<7.56 mg/day)		
			Post- or peri-menopausal women	Highest versus lowest category of intake (>13.03 g/day versus <2.12 g/day)	OR = 0.50 (0.38–0.95)	
			ER^+/PR^+	Highest versus lowest category of intake (>13.03 g/day versus <2.12 g/day)	OR = 0.63 (0.45–0.97)	

36 458 post-menopausal women. Researchers supported the hypothesis that a diet rich in isoflavones from soy products reduces the risk of post-menopausal breast cancer, particularly in populations with comparatively high excretion of phytoestrogens. Furthermore, in the Singapore Chinese Health Study, Wu et al. (2008) recruited 35 303 Singapore Chinese Women during April 1993 to December 1998. After 338 242 person-years, relative to women with lower soy intake women with higher intake showed a significant 18% risk reduction [Relative Risk (RR) = 0.82, 95% Confidence Interval (CI) = 0.70–0.97]. Similarly, in the Shanghai Women's Health Study, 73 223 Chinese women were followed-up for an average of 7.4 years. The multivariate-adjusted relative risks (RRs) for the upper intake quintile compared with the lowest quintile were 0.41 (95% CI: 0.25, 0.70) for soy protein intake and 0.44 (95% CI: 0.26, 0.73) for isoflavone intake (Lee et al., 2009).

In conclusion, regarding the above results, it is obvious that soy food and isoflavone intake seems to have a protective role against breast cancer mainly in Asian populations instead of the Westerns. It remains to be clarified further whether it happens due to the increased consumption of phytoestrogen-food by those populations or as they generally have a diet rich in vegetables and fruits, but low in animal protein. The above explanation should be taken into consideration since only few studies included in this review, have made adjustments for fruit, vegetables and animal protein intake.

Dietary fiber

The 2007 WCRF/AICR Second Expert Report (WCRF/AICR, 2007) as well as the more recent Updated Breast Cancer 2010 report (WCRF/AICR, 2010), suggested that the evidence of dietary fiber consumption in relation to breast cancer incidence, are either too limited or inconsistent for a conclusion. However, in a recent meta-analysis of 10 prospective cohort studies involving 16 848 cases and 712 895 participants, Dong et al. (2011) reported a significant inverse association of dietary fiber intake with risk of breast cancer. Similarly, Aune et al. (2012) in a more recent systematic review and meta analysis, after analyzing the data of 16 prospective studies found an inverse association between dietary fiber intake and breast cancer risk, which appeared to be more pronounced in studies with levels ($\geq$25 versus $<$25 g/day) or large ranges ($\geq$13 versus $<$13 g/day) of fiber intake.

In this review, nine prospective studies conducted the last 10 years were analyzed (Table 5). Of them, the smallest study included $n = 11\,726$ women (Mattisson et al., 2004a), whereas the largest study included $n = 185\,598$ women (Park et al., 2009). Only one out of the nine studies reported a positive association between fiber intake and breast cancer risk. In particular, Giles et al. (2006) analyzed the fiber consumption of 324 cases of breast cancer from the follow-up of 12 273 post-menopausal women from the Melbourne Collaborative Cohort Study. Results showed that an increase in fiber intake was associated with an increased risk of ER^+/PR^+ tumors. Most prospective studies reported lack of association between dietary fiber intake – either as total fiber or intake of its fractions – and breast cancer risk (Cho et al., 2003a; Holmes et al., 2004; Mattisson et al., 2004a; Terry et al., 2002; Wen et al., 2009). It should be noted that in some studies authors did not exclude the possibility that a very high fiber intake (>26–30 g/day) could contribute to decreased breast cancer risk (Holmes et al., 2004; Mattisson et al., 2004a).

There are some studies that reported inverse relationship between fiber intake and breast cancer risk. Specifically, Cade et al. (2007) studied $n = 607$ women who developed invasive breast cancer (350 post-menopausal and 257 pre-menopausal), during 240 959 person-years of follow-up in the UK Women's

Table 5. Studies on dietary fiber intake and breast cancer risk from 2002.

References	Country or region/ Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/Items	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
Terry et al. (2002)	Cohort	89 835/2536 average 16.2 years	Total fiber	Highest versus lowest quintile (25.8 g/day versus 15.2 g/day)	RR = 0.92 (0.78–1.09)	Study center, treatment allocations, age in 5-year age groups, body mass index, cigarette smoking, education level, vigorous physical activity, oral contraceptive use, hormone replacement therapy, parity, history of benign breast disease, history of breast self-exam, family history of breast cancer, menopausal status, intakes of energy, alcohol, calcium, vitamin C, vitamin E, folic acid, and saturated fat.
			Soluble fiber	Highest versus lowest quintile (7.8 g/day versus 4.6 g/day)	RR = 0.90 (0.75–1.08)	
			Insoluble fiber	Highest versus lowest quintile (5.5 g/day versus 2.8 g/day)	OR = 0.89 (0.76–1.03)	
			Cereal fiber	Highest versus lowest quintile (5.6 g/day versus 2.6 g/day)	OR = 0.90 (0.78–1.04)	
			Fruit fiber	Highest versus lowest quintile (6.6 g/day versus 2.00 g/day)	OR = 1.07 (0.92–1.25)	
			Vegetable fiber	Highest versus lowest quintile (11.0 g/day versus 5.4 g/day)	OR = 0.90 ().75–1.08)	
			Lignin	Highest versus lowest quintile (2.1 g/day versus 1.00 g/day)	OR = 0.89 (0.76–1.03)	
			Cellulose	Highest versus lowest quintile (6.9 g/day versus 3.3 g/day)	OR = 0.97 (0.83–1.14)	
Cho et al. (2003a)	Cohort	90 655/714 8 years	Total fiber	Highest versus lowest quintile	RR = 0.88 (0.67–1.14)	Stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and adjusted simultaneously for smoking, height, parity and age at first birth, BMI, age at menarche, family history of breast cancer, history of benign breast disease, oral contraceptive use, menopausal status, alcohol intake, energy intake, and animal fat intake.
			Fiber from cereals	Highest versus lowest quintile	RR = 0.91 (0.69–1.21)	
			Fiber from fruits	Highest versus lowest quintile	RR = 1.13 (0.88–1.46)	
			Fiber from vegetables	Highest versus lowest quintile	RR = 0.97 (0.75–1.24)	
			Fiber from cruciferous vegetables	Highest versus lowest quintile	RR = 0.87 (0.68–1.12)	
			Fiber from legumes	Highest versus lowest quintile	RR = 0.79 (0.62–1.02)	
			Soluble fiber	Highest versus lowest quintile	RR = 0.87 (0.67–1.13)	
			Insoluble fiber	Highest versus lowest quintile	RR = 0.81 (0.62–1.07)	
Mattisson et al. (2004a)	Cohort	11 726/342 89 602 person-years	Fiber intake	Highest versus lowest quintile (25.9 g versus 12.5 g)	IRR = 0.58 (0.40–0.84)	Diet interviewer, season of diet interview, method version, age, change of dietary habits, total energy, current hormone use, age at first child, height, waist, leisure time physical activity, age at menarche, educational level.
Holmes et al. (2004)	Cohort	88 678/4092 18 years	Fiber intake	Highest versus lowest quintile	RR = 0.98 (0.87–1.11)	Age, body mass index; 2-year time period, total energy intake; alcohol intake, parity and age at first birth; height in inches; family history of breast cancer; history of benign breast disease and age at menarche in years.
Giles et al. (2006)	Cohort	12 273/324 12 years	*Total fiber*			Age at attendance, country of birth, total energy intake and hormone replacement therapy.
			All cases	Increase of 1 SD	RR = 1.08 (0.92–1.26)	
			Non-localized	Increase of 1 SD	RR = 1.10 (0.90–1.36)	
			Localized	Increase of 1 SD	RR = 1.10 (0.91–1.33)	
			Grade I	Increase of 1 SD	RR = 1.38 (1.08–1.75)	
			Grade II	Increase of 1 SD	RR = 1.08 (0.87–1.34)	
			Grade III	Increase of 1 SD	RR = 1.03 (0.81–1.32)	

(*continued*)

Table 5. Continued

References	Country or region/ Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/Items	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
			ER^+/PR^+	Increase of 1 SD	RR = 1.36 (1.10–1.67)	
			ER^+/PR^-	Increase of 1 SD	RR = 1.01 (0.61–1.69)	
			ER^-/PR^-	Increase of 1 SD	RR = 0.65 (0.43–0.99)	
Cade et al. (2007)	Cohort	35 792/607 240 959 person years	*Pre-menopausal women*			Age, BMI, physical activity, current smoking status, oral contraceptive use, hormone replacement therapy use, number of children, alcohol intake, total energy intake corrected for measurement error.
			Total fiber	Highest versus lowest quintile (30 or more g/day versus <20 g/day)	HR = 0.48 (0.24–0.96)	
			Cereal fiber	Highest versus lowest quintile (13 or more g/day versus <4 g/day)	HR = 0.59 (0.32–1.10)	
			Fruit fiber	Highest versus lowest quintile (6 or more g/day versus <2 g/day)	HR = 0.81 (0.44–1.49)	
			Vegetable fiber	Highest versus lowest quintile (7 or more g/day versus <3 g/day)	HR = 1.26 (0.73–2.18)	
Suzuki et al. (2008)	Cohort	51 823/1188 average 8.3 years	*Total fiber intake*			Age, height , body mass index, education, parity, age at first birth, age at menarche, age at menopause, type of menopause, use of oral contraceptives, use of post-menopausal hormones, family history of breast cancer among first-degree relatives, history of benign breast disease, total energy intake, energy-adjusted total fat intake, intake of fruits and vegetables and alcohol intake.
			All invasive	Highest versus lowest quintile (>26.6 g/day versus <18.5 g/day)	RR = 0.85 (0.69–1.05)	
			ER^+/PR^+	Highest versus lowest quintile (>26.6 g/day versus <18.5 g/day)	RR = 0.85 (0.64–1.13)	
			ER^+/PR^-	Highest versus lowest quintile (>26.6 g/day versus <18.5 g/day)	RR = 0.83 (0.52–1.31)	
			ER^-/PR^-	Highest versus lowest quintile (>26.6 g/day versus <18.5 g/day)	RR = 0.94 (0.49–1.80)	
Wen et al. (2009)	Cohort	74 942/616 average 7.35 years	*Fiber intake*			Age at the start of follow-up, total energy intake, education level, BMI, age at first birth, breast cancer history in first-degree relative, personal history of benign breast diseases, and physical activity.
			All subjects	Highest versus lowest quintile	HR = 1.22 (0.94–1.58)	
			Pre-menopausal	Highest versus lowest quintile	HR = 2.01 (1.26–3.19)	
			Post-menopausal	Highest versus lowest quintile	HR = 0.98 (0.72–1.34)	
Park et al. (2009)	Cohort	185 598/5461 7 years	*Dietary fiber intake*			Race, education, BMI, age at first birth and parity, family history of breast cancer , age at menopause, physical activity , smoking, menopausal hormone therapy use , breast biopsy, gynecologic surgery, and intakes of alcohol, total fruit and vegetables, total fat and total energy.
			All breast cancer	Highest versus lowest quintile	RR = 0.87 (0.77–0.98)	
			Ductal tumors	Highest versus lowest quintile	RR = 0.90 (0.77–1.04)	
			Lobular tumors	Highest versus lowest quintile	RR = 0.66 (0.44–0.97)	
			Ductal or lobular tumors	Highest versus lowest quintile	RR = 0.83 (0.53–1.29)	
			Other tumors	Highest versus lowest quintile	RR = 0.92 (0.69–1.23)	
			ER^+/PR^+	Highest versus lowest quintile	RR = 0.95 (0.76–1.20)	
			ER^+/PR^-	Highest versus lowest quintile	RR = 0.74 (0.45–1.21)	
			ER^-/PR^-	Highest versus lowest quintile	RR = 0.56 (0.35–0.90)	

Cohort Study (UKWCS). In pre-menopausal women, a significant inverse relationship was found between total fiber intake and risk of breast cancer (p for trend = 0.01). In addition, Suzuki et al. (2008) regarding specific types of fiber, observed statistically significant risk reduction for overall (34%) and for ER^+/PR^+ (38%) tumors for the highest versus lowest quintile of fruit fiber. Moreover, among ever-users of post-menopausal hormone (PMH), total fiber intake and especially cereal fiber were statistically significantly associated with ~50% reduced risk for overall and ER^+/PR^+ tumors when comparing the highest to the lowest quartile. Recently, Park et al. (2009) examined the relationship of dietary fiber intake to breast cancer by hormone receptor status among $n = 5461$ breast cancer cases who participated in the National Institutes of Health-AARP Diet and Health Study; dietary fiber intake was inversely associated with breast cancer risk (RR = 0.87; 95% CI 0.77, 0.88; $p_{trend} = 0.02$), a relationship that seemed to be stronger for ER^-/PR^- than for ER^+/PR^+ tumors.

Conclusively, the majority of the cohort studies analyzed here seems to lack of association between dietary fiber intake and cancer risk. However, because of lack of sufficient, representative and methodologically appropriate data, further observational studies, as well as dietary interventions are needed, to confirm or refute the aforementioned results.

Dietary carbohydrates

In recent years, the consumption of dietary carbohydrates has been related to breast cancer risk due to their effect on circulating insulin levels, as elevated blood glucose levels lead to an increase in blood insulin (Gupta et al., 2002; Kaaks & Lukanova, 2001). However, serum insulin levels were shown to be inversely correlated with IGF binding protein which influences the physiologically available IGF-I. Consequently, the consumption of dietary carbohydrates which leads to an increase in blood insulin levels provoke a decreased production of IGF binding protein which in turn results to increased bioavailability of IGF-I (Conover et al., 1992; Kaaks, 1996, 2004). As IGF-I has mitogenic and antiapoptotic effects on breast cancer cells (Helle & Lonning 1996; Papa et al., 1990; Yu et al., 2003), its elevation could play a role in breast cancer development and particularly in pre-menopausal women (Hankinson et al., 1998; Kaaks, 2004; Toniolo et al., 2000; Yu et al., 2002). Moreover, many studies have shown that IGF-I and estrogens act synergistically on the pathogenesis of breast cancer, as they are strong mitogens for breast cancer cells enhancing cell growth and proliferation (Lykkesfeldt, 1997; Yee & Lee, 2000).

Many population studies concerning dietary carbohydrates intake and breast cancer risk, have measured Glycemic Index (GI) as well as Glycemic Load (GL) due to their opportunity to reflect glucose absorption and insulin response better than the absolute intake of carbohydrates alone. These studies support the theory that carbohydrate quality rather than the absolute intake of carbohydrates may play an important role in breast cancer (Jenkins et al., 2002).

In this review, 16 studies were analyzed, comprising of 13 cohorts and 3 case–controls (Table 6). The results of the majority of these studies (including 1 case–control and 10 cohort studies) have shown no association between carbohydrate intake, GI or GL and overall breast cancer risk (Cho et al., 2003a; Giles et al., 2006; Higginbotham et al., 2004; Holmes et al., 2004; Jonas et al., 2003; Lajous et al., 2008; Nielsen et al., 2005; Romieu et al., 2012; Shikany et al., 2011; Silvera et al., 2005; Yun et al., 2010). In contrast, there are some studies that reported a positive association between carbohydrates intake and breast cancer risk. First, Romieu et al. (2004) conducting a case–control study among Mexican women, reported that carbohydrate intake was positively associated with breast cancer risk overall and both for pre- and post-menopausal women. Moreover, Lajous et al. (2005), in a population-based case–control study among Mexican women again, found a direct association between dietary GL and the risk of breast cancer. Concerning cohort studies, Sieri et al. (2007) reported an increase in breast cancer risk among Italian women with a high GL diet. This greater risk was evident mostly in pre-menopausal women and those with a Body Mass Index (BMI) less than 25. Similar results were found by Wen et al. (2009) who studied 616 incident breast cancer cases among 74 942 women from the Shanghai Women's Health Study. Specifically, they proposed that a high carbohydrate intake and a diet with a high GL might be associated with breast cancer risk in pre-menopausal women or women younger than 50 years. Finally, Larsson et al. (2009a) examining 2952 incident cases of invasive breast cancer among 61 433 women of the Swedish Mammographic cohort, suggested that a high carbohydrate intake and diets with high GI and GL may increase the risk of developing ER^+/PR^- breast cancer highlighting the relationship between hormonal status of the tumor and the influence of carbohydrate intake. Conclusively, depending on the above results, there seems to be no association between carbohydrate intake, glycemic index or glycemic load and overall breast cancer risk.

Dietary lipids

The relationship between dietary fat and the risk for breast cancer has been controversial for decades. Nevertheless, there is still limited evidence suggesting that consumption of total fat is a cause of breast cancer (WCRF/AICR, 2007). In this review, we included 21 studies, 10 case–control studies, 9 cohort studies and 2 dietary interventions, which analyze the relationship between dietary fat intake and breast cancer risk (Table 7).

In the majority of the case–control studies, dietary fat intake was associated positively with the risk of breast cancer. Specifically, in 6 out of the 10 case–control studies, breast cancer was positively associated with dietary total fat intake (Freedman et al., 2006; Kallianpur et al., 2008; Sieri et al., 2002; Ward et al., 2008; Wirfalt et al., 2002), saturated fat (Alothaimeen et al., 2004; Kallianpur et al., 2008), monounsaturated fat (Freedman et al., 2006; Kallianpur et al., 2008; Wang et al., 2008; Wirfalt et al., 2002) or polyunsaturated fat (Alothaimeen et al., 2004; Freedman et al., 2006; Wirfalt et al., 2002). The remaining case–control studies reported no association of breast cancer with total and saturated fat (Do et al., 2003; Goodstine et al., 2003; Sulaiman et al., 2011; Zhang et al., 2011), monounsaturated fat (Goodstine et al., 2003; Sulaiman et al., 2011; Zhang et al., 2011) or even polyunsaturated fat (Goodstine et al., 2003; Sulaiman et al., 2011).

Cohort observational studies demonstrated, in their majority, no association between dietary fat intake and breast cancer risk. In particular, they showed no association between breast cancer and total fat (Horn-Ross et al., 2002; Kim et al., 2006; Lof et al., 2007; Park et al., 2012; Voorrips et al., 2002; Wakai et al., 2005), saturated fat (Kim et al., 2006; Lof et al., 2007; Park et al., 2012; Wakai et al., 2005), monounsaturated and polyunsaturated fat (Kim et al., 2006; Lof et al., 2007). Nevertheless, despite the among results, when Cho et al. (2003b) assessed dietary fat intake and breast cancer risk among 90 655 pre-menopausal women aged 26–46 years, they reported that relative to women in the lowest quintile of fat intake, women in the highest quintile of fat intake had a slight increased risk of breast cancer (RR = 1.25, 95% CI = 0.98 to 1.59; $p = 0.06$). Moreover, intakes of both saturated and monounsaturated fat were related to modestly elevated breast cancer risk. More recently,

Table 6. Studies on dietary carbohydrates intake and positive association with breast cancer risk from 2002.

References	Country or region/ Study design	Size of cohort/ no of cases (no. controls); years followed	Subtype of cancer/Items	Comparison of highest versus lowest category (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
Romieu et al. (2004)	Case–control	475/1391	*Carbohydrates*			Age, total energy intake, SES, family breast cancer, menopausal status, and parity.
			All women	Highest versus lowest quartile (>62% calories versus ≤52% calories)	OR = 2.22 (1.63–3.04)	
			Pre-menopausal women	Highest versus lowest quartile (>62% calories versus ≤52% calories)	OR = 2.31 (1.36–3.91)	
			Post-menopausal women	Highest versus lowest quartile (>62% calories versus ≤52% calories)	OR = 2.22 (1.49–3.30)	
Lajous et al. (2005)	Case–control	475/1391	*Glycemic load*			Age, total caloric intake, total folate intake, socioeconomic status, family breast cancer, menopausal status (only for all women), parity and availability of BMI.
			All women	Highest versus lowest quartile	OR = 1.62 (1.13–2.32)	
			Pre-menopausal	Highest versus lowest quartile	OR = 1.43 (0.81–2.53)	
			Post-menopausal	Highest versus lowest quartile	OR = 2.18 (1.34–3.55)	
			Glycemic index			
			All women	Highest versus lowest quartile	OR = 0.84 (0.62–1.15)	
			Pre-menopausal	Highest versus lowest quartile	OR = 0.66 (0.39–1.12)	
			Post-menopausal	Highest versus lowest quartile	OR = 0.81 (0.54–1.22)	
Sieri et al. (2007)	Cohort	8926/289 mean 11.5 years	*Glycemic index*			Height, weight, age at menarche, smoking status, education, parity, oral contraceptive use, energy intake, fiber intake, saturated fat intake, and alcohol intake.
			All women	Highest versus lowest quintile (>57.5 versus <53.5)	RR = 1.57 (1.04–2.36)	
			Pre-menopausal	Highest versus lowest quintile (>57.5 versus <53.5)	RR = 1.82 (1.01–3.27)	
			Post-menopausal	Highest versus lowest quintile (>57.5 versus <53.5)	RR = 1.12 (0.62–2.02)	
			Glycemic load			
			All women	Highest versus lowest quintile (>133.7 versus <103.2)	RR = 2.53 (1.54–4.16)	
			Pre-menopausal	Highest versus lowest quintile (>133.7 versus <103.2)	RR = 3.89 (1.89–8.34)	
			Post-menopausal	Highest versus lowest quintile (>133.7 versus <103.2)	RR = 1.67 (0.80–3.46)	
Wen et al. (2009)	Cohort	74 942/616 average 7.35 years	*Carbohydrate intake*			Age, at the start of follow-up, total energy intake, education level, BMI, age at first birth, breast cancer history in first-degree relative, personal history of benign breast diseases, and physical activity.
			All subjects			
			Pre-menopausal	Highest versus lowest quintile	RR = 1.22 (0.94–1.58)	
			Post-menopausal	Highest versus lowest quintile	RR = 2.01 (1.26–3.19)	
			Glycemic index	Highest versus lowest quintile	RR = 0.98 (0.72–1.34)	
			All subjects			
			Pre-menopausal	Highest versus lowest quintile	RR = 1.03 (0.79–1.34)	
			Post-menopausal	Highest versus lowest quintile	RR = 1.19 (0.73–1.94)	
			Glycemic load	Highest versus lowest quintile	RR = 0.96 (0.70–1.31)	
			All subjects			
			Pre-menopausal	Highest versus lowest quintile	RR = 1.07 (0.82–1.39)	
			Post-menopausal	Highest versus lowest quintile	RR = 1.53 (0.96–2.45)	
				Highest versus lowest quintile	RR = 0.91 (0.67–1.25)	

Larsson et al. (2009a)	Cohort	61 433/2952 mean 17.4 years	*Carbohydrate*			Age, education, body mass index, height, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of post-menopausal hormones, family history of breast cancer, and intakes of alcohol, dietary fiber and total energy.
			All invasive tumors	Highest versus lowest quintile (≥246 g/day versus <211 g/day)	RR = 1.09 (0.95–1.25)	
			ER^+/PR^+	Highest versus lowest quintile (≥246 g/day versus <211 g/day)	RR = 1.08 (0.88–1.33)	
			ER^+/PR^-	Highest versus lowest quintile (≥246 g/day versus <211 g/day)	RR = 1.34 (0.93–1.94)	
			ER^-/PR^-	Highest versus lowest quintile (≥246 g/day versus <211 g/day)	RR = 1.14 (0.73–1.79)	
			Glycemic index			
			All invasive tumors	Highest versus lowest quintile (≥83.4 versus <75.8)	RR = 1.08 (0.96–1.21)	
			ER^+/PR^+	Highest versus lowest quintile (≥83.4 versus <75.8)	RR = 0.89 (0.74–1.06)	
			ER^+/PR^-	Highest versus lowest quintile (≥83.4 versus <75.8)	RR = 1.44 (1.06–1.97)	
			ER^-/PR^-	Highest versus lowest quintile (≥83.4 versus <75.8)	RR = 1.29 (0.85–1.96)	
			Glycemic load			
			All invasive tumors	Highest versus lowest quintile (≥200 versus <164)	RR = 1.13 (1.00–1.29)	
			ER^+/PR^+	Highest versus lowest quintile (≥200 versus <164)	RR = 0.94 (0.77–1.13)	
			ER^+/PR^-	Highest versus lowest quintile (≥200 versus <164)	RR = 1.81 (1.29–2.53)	
			ER^-/PR^-	Highest versus lowest quintile (≥200 versus <164)	RR = 1.23 (0.79–1.90)	

Table 7. Studies on fat intake and breast cancer risk from 2002.

References	Study design	Size of cohort/ no of cases (no. controls); years followed	Type of fat intake	Comparison of highest versus lowest quantile (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
Sieri et al. (2002)	Nested case–control	3367/56 (214 controls)	Total	H versus l tertile (≥62.8 versus <54.3 g)	RR = 3.47 (1.43–8.44)	BMI, energy intake, parity, place of birth, level of education, total fat (for all analyses except total fat).
			Animal	H versus. l tertile (≥36.3 versus <27.6 g)	RR = 1.84 (0.63–5.43)	
			Vegetable	H versus l tertile (≥30.0 versus <22.3 g)	RR = 0.88 (0.29–2.66)	
			SFA	H versus l tertile (≥22.2 versus <18.3 g)	RR = 1.12 (0.31–4.04)	
			MUFA	H versus l tertile (≥30.0 versus <23.5 g)	RR = 2.96 (0.70–12.6)	
			PUFA	H versus l tertile (≥7.7 versus <6.3 g)	RR = 2.03 (0.68–6.03)	
			Linoleic	H versus l tertile (≥6.18 versus <5.07 g)	RR = 1.39 (0.51–3.80)	
			Linolenic	H versus l tertile (≥0.99 versus <0.86 g)	RR = 0.71 (0.20–2.55)	
Voorrips et al. (2002)	Nested case–control	62 573/941 (1598 controls)	Total	H versus l quintile (median 86 versus 61 g/day)	RR = 1.13 (0.84–1.52)	BMI, family predisposition, history of benign breast disease, age at menarche, age at menopause, oral contraceptive use, parity, age at first childbirth, education, alcohol use, current cigarette smoking, total energy intake, total adjusted fat intake.
			Animal	H versus l quintile (median 71 versus 35 g/day)	RR = 1.05 (0.79–1.04)	
			Vegetable	H versus l quintile (median 38 versus 5 g/day)	RR = 1.02 (0.75–1.38)	
			SFA	H versus l quintile (median 38 versus 22 g/day)	RR = 1.40 (0.97–2.03)	
			MUFA	H versus l quintile (median 27 versus 18 g/day)	RR = 0.61 (0.38–0.96)	
			PUFA	H versus l quintile (median 24 versus 8 g/day)	RR = 0.88 (0.65–1.21)	
			Trans-unsaturated	H versus l quintile (median 3.6 versus 1.5 g/day)	RR = 1.30 (0.93–1.80)	
Horn-Ross et al. (2002)	Cohort	111 526/711 3 years	Total	H versus l quintile (no information given)	RR = 0.8 (0.6–1.2)	BMI, family predisposition, race, daily caloric intake, age at menarche, nulliparity/age at first full-term pregnancy, physical activity, interaction for BMI and menopausal status.
			SFA	H versus l quintile (no information given)	RR = 0.8 (0.6–1.2)	
			MUFA	H versus l quintile (no information given)	RR = 0.9 (0.6–1.2)	
			PUFA	H versus l quintile (no information given)	RR = 0.9 (0.7–1.3)	
Cho et al. (2003b)	Cohort	90 655/714 8 years	Total	H versus l quintile (median 38% versus 24% of energy	RR = 1.25 (0.98–1.59)	BMI, family predisposition, smoking, height, parity and age at first birth, age at menarche, history of benign breast disease, oral contraceptive use, menopausal status, alcohol intake, energy, protein.
			Animal	H versus l quintile (median 23% versus 12% of energy	RR = 1.33 (1.02–1.73)	
			Vegetable	H versus l quintile (median 19% versus 9% of energy	RR = 0.97 (0.76–1.24)	
			SFA	H versus l quintile (median 14% versus 8% of energy	RR = 1.06 (0.74–1.53)	
			MUFA	H versus l quintile (median 15% versus 9% of energy	RR = 1.10 (0.75–1.62)	
			PUFA	H versus l quintile (median 7% versus 4% of energy	RR = 0.96 (0.73–1.27)	
			Trans-unsaturated	H versus l quintile (median 2.3% versus 0.9% of energy	RR = 0.96 (0.70–1.31)	
Do et al. (2003)	Case–control	224/250	Total	>75 versus <25 percentile (≥49.2 versus <29.5 g/day)	OR = 1.15 (0.58–2.41)	BMI, age at menarche, family history of breast cancer, pregnancy, total number of
			Total-saturated	>75 versus <25 percentile (≥19.5 versus	OR = 1.65 (0.92–2.45)	

				<10.7 g/day)		full term delivery, total periods of breast feeding, total energy intake.
			Total-unsaturated	>75 versus <25 percentile (≥29.2 versus <18.8 g/day)	OR = 1.02 (0.86–1.64)	
			Cholesterol	>75 versus <25 percentile (≥230.9 versus <115.3 mg/day)	OR = 1.32 (0.67–1.98)	
Goodstine et al. (2003)	Case–control	565/554	Total	H versus l quartile (>78.0 versus ≤42.6 g/day)	OR = 1.08 (0.64–1.84)	Age, age at menarche, age at first birth, number of live births, lactation history, BMI, menopausal status, race, family history of breast cancer and income.
			Total SFA	H versus l quartile (>28.3 versus ≤14.8 g/day)	OR = 0.97 (0.59–1.58)	
			Total MUFA	H versus l quartile (>27.7 versus ≤15.1 g/day)	OR = 1.17 (0.70–1.95)	
			Total PUFA	H versus l quartile (>16.6 versus ≤9.2 g/day)	OR = 1.06 (0.68–1.64)	
			EPA	H versus l quartile (>0.06 versus ≤0.01 g/day)	OR = 0.94 (0.66–1.34)	
			DHA	H versus l quartile (>0.13 versus ≤0.04 g/day)	OR = 1.00 (0.70–1.44)	
			Ratio $(n-3)/(n-6)$	H versus l quartile (>0.31 versus ≤0.11 g/day)	OR = 0.82 (0.58–1.15)	
Mattisson et al. (2004a)	Cohort	11 726/342 89 602 person-years	Total	H versus l quintile (mean 45.4% versus 29.6% of total energy)	RR = 1.36 (0.96–1.94)	Energy, interviewer, season of diet interview, change of dietary habits, height, weight, current hormone use, age at birth of first child, age at menarche, physical activity, smoking, drinking, education.
Wakai et al. (2005)	Cohort	26 291/129 mean 7.6 years	Total fat	H versus l quartile (≥24.55 versus <18.44% of energy)	RR = 0.80 (0.46–1.38)	Age, study area, educational level, family history of breast cancer, age at menarche, age at menopause, age at first birth, parity, use of exogenous female hormones, alcohol consumption, smoking, consumption of green leafy vegetables, daily walking, height, BMI, total energy intake.
			Animal fat	H versus l quartile (≥11.79 versus <7.41% of energy)	RR = 0.61 (0.36–1.06)	
			Vegetable fat	H versus l quartile (≥10.92 versus <7.83% of energy)	RR = 1.21 (0.72–2.02)	
			Fish fat	H versus l quartile (≥3.27 versus <1.41% of energy)	RR = 0.56 (0.33–0.94)	
			SFA	H versus l quartile (≥7.45 versus <5.25% of energy)	RR = 0.68 (0.40–1.15)	
			MUFA	H versus l quartile (≥7.55 versus <5.50% of energy)	RR = 0.62 (0.36–1.09)	
			PUFA	H versus l quartile (≥6.03 versus <4.39% of energy)	RR = 1.10 (0.63–1.90)	
			$n-3$ fatty acids	H versus l quartile (≥1.32 versus <0.86% of energy)	RR = 0.69 (0.40–1.18)	
			$n-6$ fatty acids	H versus l quartile (≥4.78 versus <3.46% of energy)	RR = 1.02 (0.59–1.74)	
			$n-6/n-3$ ratio	H versus l quartile (≥4.61 versus <3.25% of energy)	RR = 1.31 (0.78–2.19)	
			Long-chain $n-3$ fatty acids	H versus l quartile (≥0.61 versus <0.29% of energy)	RR = 0.50 (0.30–0.85)	
Kim et al. (2006)	Cohort	80 375/3537 20 years	Total	Not reported	RR = 0.98 (0.95–1.00)	Energy, age, alcohol intake, time period, height, parity, age at first birth, weight change
			Animal fat	Not reported	RR = 0.98 (0.95–1.01)	
			Vegetable fat	Not reported	RR = 0.99 (0.95–1.04)	

(*continued*)

Table 7. Continued

References	Study design	Size of cohort/ no of cases (no. controls); years followed	Type of fat intake	Comparison of highest versus lowest quantile (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
			PUFA	Not reported	RR = 0.94 (0.92–1.08)	since age 18 years, BMI at age 18 years, age at menopause, use of hormone replacement therapy, family history of breast cancer, benign breast disease, age at menarche.
			SFA	Not reported	RR = 0.93 (0.87–1.00)	
			MUFA	Not reported	RR = 0.94 (0.88–1.01)	
			Trans-unsaturated fat	Not reported	RR = 0.96 (0.90–1.03)	
			Long-chain omega-3 fatty acids	Not reported	RR = 1.00 (1.00–1.01)	
			α-Linolenic acid	Not reported	RR = 1.00 (0.99–1.00)	
			Cholesterol	Not reported	RR = 1.00 (0.99–1.00)	
				Not reported		
Thiebaut et al. (2007)	Cohort	188 736/3501 mean 4.4 years	Total	H versus l quintile (median 90.5 versus 24.2 g/day)	RR = 1.22 (1.03–1.45)	Alcohol, non-alcohol energy intakes, smoking history, combined age at birth of first child and number of children, age at menopause, menopausal hormone use, BMI.
			SFA	H versus l quintile (median 13.2 versus 5.8% energy)	RR = 1.18 (1.06–1.31)	
			MUFA	H versus l quintile (median 15.2 versus 7.2% energy)	RR = 1.12 (1.00–1.24)	
			PUFA	H versus l quintile (median 10.3 versus 4.5% energy)	RR = 1.12 (1.01–1.25)	
			Total	Continuous variable; 2-fold increase	RR = 1.15 (1.05–1.26)	
			SFA	Continuous variable; 2-fold increase	RR = 1.13 (1.05–1.22)	
			MUFA	Continuous variable; 2-fold increase	RR = 1.12 (1.03–1.21)	
			PUFA	Continuous variable; 2-fold increase	RR = 1.10 (1.01–1.20)	
Lof et al. (2007)	Cohort	49 261/974 mean 13 years	Total (entire cohort)	H versus l quintile (median 34 versus 26% energy)	HR = 1.02 (0.72–1.45)	BMI, alcohol intake, education, parity, age menarche, use of oral contraceptives, age at first, birth, first-degree relative with breast cancer, non-alcohol total energy intake and total fat intake.
			MUFA (entire cohort)	H versus l quintile (median 11 versus 9% energy)	HR = 0.88 (0.53–1.46)	
			PUFA (entire cohort)	H versus l quintile (median 4.8 versus 3.6% energy)	HR = 0.72 (0.52–1.00)	
			SFA (entire cohort)	H versus l quintile (median 0.65 versus 11% energy)	HR = 1.12 (0.69–1.81)	
			Total (breast cancer before 50 years)	H versus l quintile (median 34 versus 26% energy)	HR = 1.46 (0.87–2.47)	
			MUFA (breast cancer before 50 years)	H versus l quintile (median 11 versus 9% energy)	HR = 1.69 (0.81–3.51)	
			PUFA (breast cancer before 50 years)	H versus l quintile (median 4.8 versus 3.6% energy)	HR = 1.06 (0.64–1.75)	
			SFA (breast cancer before 50 years)	H versus l quintile (median 17 versus 11% energy)	HR = 0.93 (0.56–1.88)	
			Total (breast cancer after 50 years)	H versus l quintile (median 34 versus 27% energy)	HR = 0.76 (0.47–1.22)	
			MUFA (breast cancer after 50 years)	H versus l quintile (median 11 versus 9% energy)	HR = 0.45 (0.25–0.99)	
			PUFA (breast cancer after 50 years)	H versus l quintile (median 4.9 versus 3.6% energy)	HR = 0.54 (0.35–0.85)	
			SFA (breast cancer after 50 years)	H versus l quintile (median 16 versus 11% energy)	HR = 1.29 (0.66–2.50)	
			Total (entire cohort)	Continuous variable; 10 g/day increase	HR = 1.04 (0.97–1.11)	
			MUFA (entire cohort)	Continuous variable; 10 g/day increase	HR = 0.82 (0.49–1.35)	
			PUFA (entire cohort)	Continuous variable; 10 g/day increase	HR = 0.83 (0.54–1.27)	

			SFA (entire cohort)	Continuous variable; 10 g/day increase	HR = 1.12 (0.84–1.49)	
			Total (breast cancer before 50 years)	Continuous variable; 10 g/day increase	HR = 1.06 (0.96–1.18)	
			MUFA (breast cancer before 50 years)	Continuous variable; 10 g/day increase	HR = 1.31 (0.63–2.73)	
			PUFA (breast cancer before 50 years)	Continuous variable; 10 g/day increase	HR = 1.31 (0.79–2.46)	
			SFA (breast cancer before 50 years)	Continuous variable; 10 g/day increase	HR = 0.81 (0.53–1.23)	
			Total (breast cancer after 50 years)	Continuous variable; 10 g/day increase	HR = 1.01 (0.93–1.11)	
			MUFA (breast cancer after 50 years)	Continuous variable; 10 g/day increase	HR = 0.55 (0.28–1.09)	
			PUFA (breast cancer after 50 years)	Continuous variable; 10 g/day increase	HR = 0.58 (0.32–1.05)	
			SFA (breast cancer after 50 years)	Continuous variable; 10 g/day increase	HR = 1.45 (0.99–2.12)	
Kallianpur et al. (2008)	Case–control	3452/3474	*Pre- and post-menopausal combined*			Age, education, BMI, WHR, age at menarche, age at first live birth, family combined history of breast cancer, regular exercise, total energy intake, study phase, age at menopause.
			Total fat	Not reported	OR = 1.10 (0.92–1.13)	
			Animal source fat	Not reported	OR = 1.34 (1.14–1.58)	
			Plant source fat	Not reported	OR = 0.70 (0.60–0.83)	
			SFA	Not reported	OR = 1.20 (1.01–1.42)	
			PUFA	Not reported	OR = 0.93 (0.79–1.10)	
			MUFA	Not reported	OR = 1.32 (1.12–1.56)	
			Pre-menopausal			
			Total fat	Not reported	OR = 1.04 (0.82–1.32)	
			Animal source fat	Not reported	OR = 1.19 (0.96–1.47)	
			Plant source fat	Not reported	OR = 0.77 (0.62–0.96)	
			SFA	Not reported	OR = 1.13 (0.90–1.42)	
			PUFA	Not reported	OR = 1.00 (0.79–1.25)	
			MUFA	Not reported	OR = 1.21 (0.97–1.51)	
			Post-menopausal			
			Total fat	Not reported	OR = 1.19 (0.90–1.57)	
			Animal source fat	Not reported	OR = 1.57 (1.22–2.02)	
			Plant source fat	Not reported	OR = 0.63 (0.48–0.81)	
			SFA	Not reported	OR = 1.28 (0.99–1.66)	
			PUFA	Not reported	OR = 0.89 (0.68–1.15)	
			MUFA	Not reported	OR = 1.49 (1.15–1.94)	
Wang et al. (2008)	Case–control	1703/2045	Total fat	H versus l quintile (not reported)	OR = 1.35 (1.10–1.65)	Age, race/ethnicity, menopausal status, country of birth, education, family history of breast cancer, history of benign breast, disease, age at menarche, parity, breast feeding, BMI, height, alcohol intake and total energy intake.
			SFA	H versus l quintile (not reported)	OR = 1.07 (0.88–1.30)	
			Linoleic	H versus l quintile (not reported)	OR = 1.27 (1.04–1.54)	
			Oleic	H versus l quintile (not reported)	OR = 1.43 (1.17–1.76)	
Sieri et al. (2008)	Cohort	319 826/7119 mean 8.8 years	Total	H versus l quintile (median 90.5 versus 24.2 g/day)	HR = 1.02 (0.90–1.17)	Age, center, educational attainment, smoking status, height, weight, alcohol intake, menopausal status.
				Continuous variable; 20% increase	HR = 1.02 (0.99–1.04)	
			SFA	H versus l quintile (median 90.5 versus 24.2 g/day)	HR = 1.13 (1.00–1.27)	
				Continuous variable; 20% increase	HR = 1.02 (1.00–1.04)	
			MUFA	H versus l quintile (median 90.5 versus 24.2 g/day)	HR = 1.05 (0.92–1.02)	
				Continuous variable; 20% increase	HR = 1.02 (0.99–1.04)	
			PUFA	H versus l quintile (median 90.5 versus 24.2 g/day)	HR = 0.97 (0.88–1.07)	
				Continuous variable; 20% increase	HR = 0.99 (0.98–1.01)	

(*continued*)

Table 7. Continued

References	Study design	Size of cohort/ no of cases (no. controls); years followed	Type of fat intake	Comparison of highest versus lowest quantile (quantity of intake)	Breast cancer risk (95% CI)	Adjustment for confounding variables
Zhang et al. (2011)	Case–control	438/438	Total fat	H versus l quartile	OR = 0.82 (0.50–1.32)	Age at menarche, live births and age at first live birth, months of breastfeeding, BMI, history of benign breast disease, mother/sister/daughter with breast cancer, physical activity, passive smoking, and total energy intake and intakes of other fatty acids simultaneously.
			SFA	H versus l quartile	OR = 0.69 (0.33–1.46)	
			MUFA	H versus l quartile	OR = 0.78 (0.37–1.66)	
			PUFA	H versus l quartile	OR = 0.50 (0.27–0.93)	
			$n-3$ polyunsaturated fat	H versus l quartile	OR = 0.73 (0.39–1.39)	
			$n-6$ polyunsaturated fat	H versus l quartile	OR = 0.86 (0.43–1.74)	
Sulaiman et al. (2011)	Case–control	382/382	Total fat	Q4 versus Q1	OR = 0.76 (0.23–2.45)	Age, ethnicity, marital status, education, working status, household income, age of menarche, pregnancy history, age at first childbirth, number of live birth, history of breastfeeding, duration of breastfeeding, history of oral contraceptive usage, smoking habits, alcohol consumption, physical activity level, family history of breast cancer, BMI, and energy intake.
			SFA	Q4 versus Q1	OR = 1.43 (0.51–3.98)	
			MUFA	Q4 versus Q1	OR = 0.96 (0.34–1.72)	
			PUFA	Q4 versus Q1	OR = 0.64 (0.23–1.73)	
			$n-3$ polyunsaturated	Q4 versus Q1	OR = 1.10 (0.49–2.48)	
			ALA	Q4 versus Q1	OR = 1.20 (0.51–2.84)	
			EPA	Q4 versus Q1	OR = 1.18 (0.54–2.60)	
			DHA	Q4 versus Q1	OR = 0.66 (0.29–1.51)	
			$n-6$ polyunsaturated	Q4 versus Q1	OR = 0.67 (0.24–1.84)	

Thiebaut et al. (2007) demonstrated similar results in the National Institutes of Health-AARP Diet and Health Study, a US cohort comprising 188 736 post-menopausal women. Indeed, they found a positive association between both total fat intake and all fat subtypes intake and breast cancer risk [Hazard Ratio (HR) of total fat intake = 1.11, 95% CI = 1.00 to 1.24; $p = 0.017$]. Finally, Sieri et al. (2008) in a large ($n = 319\,826$), geographically and culturally heterogeneous cohort of European women enrolled in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, reported a weak positive association between saturated fat intake and breast cancer risk.

The positive association between dietary fat intake and breast cancer was demonstrated by two more cohort studies, which were trying to identify a food pattern and relate this to breast cancer. First, in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort, Schulz et al. (2008) followed 15 351 female subjects aged 35–65 years old for an average of 6 years. A food pattern characterized by high-fat food choices was significantly associated with increased risk of breast cancer. Respectively, when Mattisson et al. (2004b) followed-up a subsample of 11 726 post-menopausal women in the Malmo Diet and Cancer cohort supported the hypothesis that a dietary pattern characterized by high fiber and low fat intakes is associated with a lower risk of post-menopausal breast cancer. High fiber consumption may reduce estrogen concentration by decreasing intestinal re-absorption, a fact that is important since high endogenous estrogen levels after menopause are a known cause of breast cancer (Kaaks et al., 2005; Key et al., 2002).

Randomized trials with breast cancer end points provide the most rigorous data about the effect of modifying risk factors including dietary lipids. A large clinical trial was conducted by Prentice et al. (2006) including 48 835 post-menopausal healthy women. They were randomly assigned to either a dietary intervention group (with significantly lower dietary fat) or a comparison group. After an average follow up of 8.1 years, the authors found that breast cancer incidence was approximately 9% lower in the dietary intervention group than in the comparison group (HR = 0.91; 95% CI, 0.83–1.01; $p = 0.09$), although the difference was not statistically significant. In contrast, recently Martin et al. (2011) recruited 4690 women with extensive mammographic density and randomized them to an intervention group (with significantly lower dietary fat) or a comparison group. There was in the intervention group a trend to a higher risk of breast cancer (adjusted hazard ratio = 1.19, 95% CI: 0.91–1.55). As a result, the authors suggested that a sustained reduction in dietary fat did not reduce breast cancer in women with extensive mammographic density.

A possible mechanism by which dietary fat could be associated with breast cancer includes endogenous estrogen levels. Specifically, dietary fat is relatively well established as a cause of increased endogenous estrogen production (Boyd et al., 2003; Bruning & Bonfrer 1986; Wu et al., 1999). Higher levels of circulating estrogens may increase risk of some types of breast cancers in women, via particularly estradiol, the most biologically active of all naturally produced estrogens. Estradiol is reported to affect cell proliferation and breast cancer development through receptor dependent and independent mechanisms by up-regulating aberrant proliferation and development of breast cancer (Davis et al., 1998). Furthermore, estrogens may affect breast cancer development independent of receptor mechanisms though structural/functional alterations in DNA (Davis et al., 1998).

In conclusion, the dietary fat–breast cancer relationship has been a topic of controversy for >20 years, with positive associations seen in animal studies and case–control studies, but no associations seen in most cohort studies. Moreover, the results of the dietary interventions conducted until now, remain controversial. In the light of these discordant or contradictory results, further studies on the relationship between breast cancer and total dietary fat consumption, and on that concerning subtypes of fat are warranted.

Dietary patterns

According to the 2007 WCRF/AICR Second Expert Report (WCRF/AICR, 2007) followed by the Updated Breast Cancer 2010 Report (WCRF/AICR, 2010), the available data concerning dietary patterns and breast cancer risk were either of too low quality, too inconsistent or the number of studies too few to allow conclusions to be reached, both for pre- and post-menopausal women. Nevertheless, dietary patterns do warrant further discussion, since it is accepted during the last years that people do not eat isolated nutrients, but they consume meals consisting of a variety of foods with complex combinations of micro- and macronutrients. As a result, several investigators still evaluate dietary patterns in relation to breast cancer. In the most recent published review and meta-analysis which examined this association, Brennan et al. (2010) analyzed 18 studies (10 cohorts and 8 case–controls) to identify the most common patterns of dietary consumption. An increase in the risk of breast cancer was shown for the highest compared with the lowest categories of a drinker dietary pattern [Odds Ratio (OR) = 1.21; 95% CI: 1.04, 1.41; $p = 0.01$]. Moreover, there was evidence of a decrease in the risk of breast cancer in the highest compared with the lowest categories of prudent/healthy dietary patterns (OR = 0.89; 95% CI: 0.82, 0.99; $p = 0.02$), while there was no evidence of a difference in the risk of breast cancer between the highest and the lowest categories of Western/unhealthy dietary patterns (OR = 1.09; 95% CI: 0.98, 1.22; $p = 0.12$). Similarly, when Edefonti et al. (2009) analyzed 19 articles published between 1995 and 2008 that identified dietary patterns defined *a priori* and *a posteriori*, reported a possible inverse association between breast cancer and a dietary pattern characterized by vegetables, fruit, legumes, whole cereals, fish, fowl and foods with a low fat content.

At this point, it is important to highlight methodological issues and differences in the way studies are carried out during the investigation of dietary patterns in relation to breast cancer risk. The dietary assessment methods used, which vary between the studies, and their validity and reproducibility, as well as the number of food items and whether they should be collapsed into a smaller number for entry into the analysis should be taken firstly into account. Furthermore, the quantification of the input variables as well as the methodology used to define dietary patterns (exploratory/*a posteriori* approach, hypothesis-oriented/*a priori* approach or reduced rank regression) should also be given the appropriate attention, in order to achieve a fair comparison of different sets of dietary patterns.

Conclusions and future directions

In this work, the relationship between specific food groups and food nutrients with breast cancer incidence was investigated through a systematic way. The analysis revealed, in accordance with the 2007 WCRF/AICR report (WCRF/AICR, 2007) as well as the Updated Breast Cancer Report 2010 (WCRF/AICR, 2010), that no consistent and statistically strong association has been established between breast cancer incidence and dietary factors, except for alcohol. Furthermore, soy food and isoflavone intake seemed to have a protective role against breast cancer incidence, mainly in Asian populations instead of the Westerns. These results are in agreement with the most recent meta-analysis which explored the association of soyfood intake with breast cancer risk. Specifically,

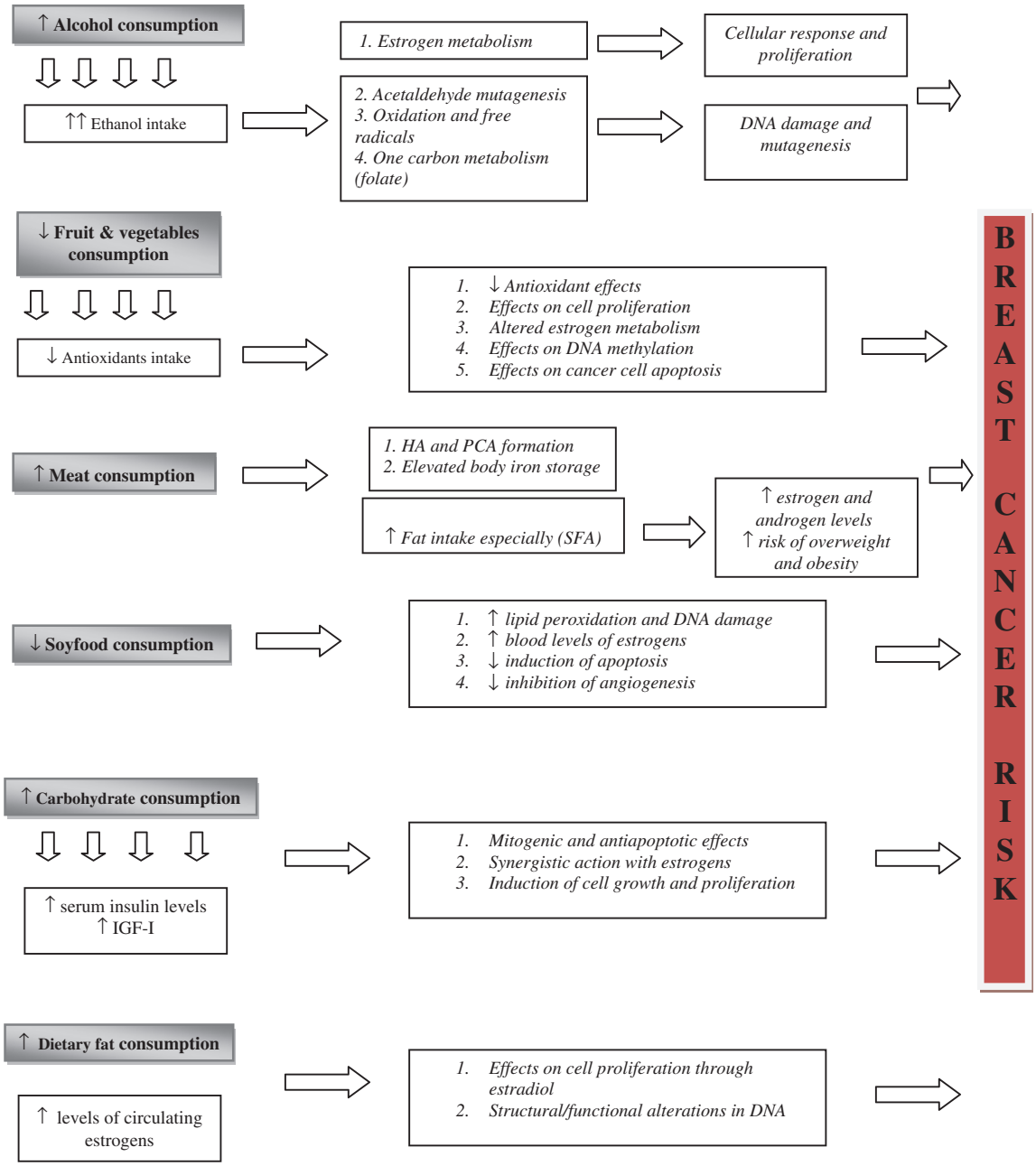

Figure 1. Hypothesized mechanistic relations between dietary variables and breast cancer.

the researchers after analyzing 23 case–controls and 5 cohort studies concluded that soyfood intake is inversely associated with the risk of breast cancer among Asian women (Zhong & Zhang, 2012). No association seems to be reported for the consumption of dietary carbohydrates, glycemic index or glycemic load and breast cancer risk, as well as for dietary fiber intake and the risk of the disease. In contrast, the evidence concerning the consumption of dietary fat, although limited, is probably suggestive of an increase in breast cancer risk, a fact that is in accordance with the 2007 WCRF/AICR report (WCRF/AICR, 2007). Finally, studies that have evaluated the role of fruit and vegetable, as well as meat intake and breast cancer incidence provide inconsistent results. Possible causes for these inconsistent results include differences in experimental designs, differences in habits among study populations, the lack of sufficient follow-up as well as methodological problems in the assessment tools used in each study (Michels et al., 2007; WCRF/AICR, 2007). In the light of these inconsistent results, the relationship between all food groups referred above and breast cancer risk merits further research which should be orientated towards the analysis of nutrition patterns rather than specific foods or micronutrients. During the past three decades, studies in different population groups have documented the protective role of the main characteristics of Mediterranean Diet (healthy/prudent dietary pattern) in the prevention of cancer overall (Kontou et al., 2011; La Vecchia, 2009; Sofi et al., 2008; Tyrovolas & Panagiotakos, 2010) while associations have been also observed between dietary patterns and the risk of renal, gastric and colorectal cancers (Handa & Kreiger, 2002; Kim et al., 2004, 2005). However, the associations of different dietary patterns with breast cancer remain unclear, as it is also reported by the above review, a fact that could easily be attributed to the methodological issues referred earlier.

In this work, an attempt to summarize the current scientific evidence regarding the association between diet and breast cancer risk was performed, based on a thorough review in the literature (Figure 1). Despite the aforementioned associations, a message carried out here was the emerging need for well-designed, large-scale observational and intervention studies that could possibly

shed light on the association between diet and breast cancer, and probably offer additional means when targeting on the prevention of breast cancer.

Declaration of interest

The authors report no conflicts of interest.

Authorship contribution

Niki Mourouti contributed to the conception and design of the paper, to the drafting of the paper and took part in the acquisition and interpretation of data. Meropi D. Kontogianni contributed to the conception and design of the paper and critically reviewed it for important intellectual content. Christos Papavagelis contributed to the conception and design of the review paper. Demosthenes B. Panagiotakos had the review concept and design, had the supervision of the paper, critically reviewed its content and gave the final approval of the version to be published. All authors have approved this version to be published.

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