ANTICANCER RESEARCH *34*: 6861-6876 (2014)

Review

The Role of Dietary Factors in Prevention and Progression of Breast Cancer

ROBERTA ELISA ROSSI[1,2], MARINOS PERICLEOUS[1], DALVINDER MANDAIR[1,3], TARA WHYAND[4] and MARTYN EVAN CAPLIN[1]

[1]Centre for Gastroenterology and [4]Department of Nutrition & Dietetics, Royal Free Hospital, London, U.K.; [2]Gastroenterology and Endoscopy Unit, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico and Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy; [3]Cancer Institute, University College London, London, U.K.

Abstract. *Background/Aim: Breast cancer (BC) is the leading global cause of cancer-related death in women. There is growing evidence for a role for dietary factors in BC pathophysiology. The aim of the present review was to evaluate the impact of dietary factors in BC risk. Materials and Methods: Bibliographical searches were performed in PubMed, using the following terms: "nutrition and breast cancer", "nutrition and breast carcinoma", "dietary factors and breast cancer", "risk factors and breast cancer", "diet and breast cancer, "breast cancer epidemiology", "breast cancer and prevention". Results: Consumption of well-done red meat appears to be associated with increased risk of BC, whereas fish may be protective. Total cholesterol, triglyceride levels and glycaemic load should be monitored and controlled in at risk populations because they may be associated with increased risk of BC, although the exact mechanisms involved are not clear. Alcohol intake should be minimized since it is a risk factor for BC. High intake of polyphenol/phyto-oestrogen -rich food (i.e. flavonoids, soya products), as well as fibres, fruits and vegetables, may have potential protective effects against BC occurrence but the results might vary according to hormonal status. Vitamin D supplements appear protective against BC development and similarly other vitamins and oligo-elements might decrease BC risk, although further large prospective studies are required. Conclusion: There exist increasing evidence that dietary factors can play an important role in both the development and prevention of BC. Large randomized clinical and epidemiological studies are required but are difficult to design due to the number of variable factors.*

Correspondence to: Professor Martyn Evan Caplin, Centre for Gastroenterology, Royal Free Hospital, Pond Street, London, NW3 2QG, U.K. Tel: +44 2078302867, Fax: +44 2074726728, e-mail: m.caplin@ucl.ac.uk

Key Words: Breast cancer, nutrition, diet, carcinogenesis, prevention review.

Breast cancer (BC) is currently the most frequently diagnosed cancer and the leading global cause of cancer-related death in women, accounting for 23% of cancer diagnoses (1.38 million women) and 14% of cancer deaths (458,000 women) each year (1). According to the American Cancer Society, the five-year relative survival rate for BC in women has improved from 63% in the early 1960s to 90% currently (2). However, BC survivors have a far higher risk of recurrence, as well as new primary BC compared to general population (3).

The identification of potentially modifiable risk factors for BC is, therefore, urgently needed. Traditionally recognized risk factors for BC include a family history of BC, early menstruation, late onset of menopause, elder age, age at first pregnancy over 30 years, infertility and not having children, use of contraceptives, hormonal treatment after menopause, no history of breastfeeding, overweight and obesity (4). Upper body obesity has been reported to be related to an aggressive tumour phenotype and a poor prognosis regardless of the menopausal status. The association between obesity and risk of BC seems to be due to increased oestrogen production by adipose tissue, to leptin and adiponectin production, and to obesity-related hyperinsulinemia (5).

There is growing evidence for a plausible role for dietary factors in BC pathophysiology but evidence in the literature is still inconclusive (6, 7).

Herein, we review the impact of different dietary components on the prevention and progression of BC.

Materials and Methods

Bibliographical searches were performed in PubMed using the following keywords, including both medical subject heading (MeSH) terms and free language words/phrases: "nutrition and breast cancer", "nutrition and breast carcinoma", "dietary factors and breast cancer", "risk factors and breast cancer", "diet and breast cancer, "breast cancer epidemiology", "breast cancer and prevention". PubMed was used to search for all relevant articles published from 1975 to 2013. Reference lists from studies selected by the electronic search were manually searched to identify further relevant reports. Reference lists from all available review articles, primary studies and proceedings of major meetings were also considered. Articles published as abstracts were included, whereas non-English language papers were excluded. The quality and strength level of the results were considered and we focused the review on meta-analyses and systemic reviews, large epidemiological studies and, where available, randomized control trials. Information on clinical trials was sourced from URL: http://clinicaltrials.gov/.

Results

A very large number of results were returned for each of our search parameters. Nutrition and breast cancer led to 2,572 hits, nutrition and breast carcinoma had 2,035, dietary factors and breast cancer 2,987, risk factors and breast cancer 28,065, diet and breast cancer 4,377, breast cancer epidemiology 45,479 and breast cancer and prevention 25,282. After filtering for year range, human studies and article type, the numbers fell to 568, 498, 766, 5,180, 1,012, 5,743 and 5,808, respectively.

After we manually screened for full-text articles and for documents, which were specific for the scope of this systematic review and we removed the duplicates, we identified a total of 175 pertinent articles with the strongest level of evidence. In more detail, we considered 18 articles for "Proteins", 18 articles for "Carbohydrate", 18 articles for "Dietary Fat", 33 articles for "Polyphenols and phyto-oestrogen", 18 articles for "Fruits and vegetables", 11 articles for "Lycopenes", 44 articles for "Vitamins and oligo-elements" and 8 articles for "Alcohol".

Proteins

Meat. Red meat, depending on processing methods, may be a source of heterocyclic amines, N-nitroso compounds and poly-aromatic hydrocarbons, all of which have been linked to carcinogenesis (8). Oral administration of 2-amino- 1-methyl-6-enylimidazo[4,5b]pyridine (PhIP), the most abundant carcinogenic heterocyclic amine in cooked meats, has been shown to induce mammary tumours in rats (9). Zheng and co-workers (10) showed that the consumption of well-done meats was associated with an elevated risk of BC in a dose-responsive manner, whereas the intake of red meat was only weakly associated with the risk of BC in the cohort of 34,388 post-menopausal women of the Iowa Women's Health Study (11). According to these results, heterocyclic amines and other compounds, including polycyclic aromatic hydrocarbons formed during high temperature cooking of animal foods, may be risk factors for BC. Some studies found a positive association between high intake of fried meats and BC with an increased risk up to 80% (12, 13). Recent studies have suggested that fats, found in red and processed meats by induction of lipid peroxidation mediated by free radicals, may be another mechanism by which processed red meat may promote carcinogenesis (14, 15). Although it has been reported that heterocyclic amines deriving from red meats contain mutagenic and carcinogenic compounds (8), a recent meta-analysis did not demonstrate an independent association (16). It has been proposed that grilled or roasted meat consumption is associated with increased risk of BC and its recurrence is due to exposure to heterocyclic amines, polycyclic aromatic hydrocarbons and other potent carcinogens (17).

Emerging evidence indicates that this dietary variable may act differently according to hormonal status (*i.e.* pre-menopausal women as opposed to their post-menopausal counterparts) and this different risk should be highlighted in cancer guidelines. A recent meta-analysis has shown that red meat may contribute to BC risk in the pre-menopausal population, whereas in the post-menopausal population the increased risk may be due to other confounders, such us increased adiposity (18). In a recent prospective cohort study, including 88,803 pre-menopausal women from the Nurses' health Study II who completed a questionnaire on diet in 1991, 2,830 cases of BC during 20 years of follow-up were documented and higher intake of total red meat was reported to be associated with an increased risk of BC overall. Additionally, higher intake of poultry, fish, eggs, legumes and nuts were not related to BC overall, which suggested that replacing red meat with a combination of legumes, poultry, nuts and fish may reduce the risk of BC, also according to hormonal status (19).

Conclusion: Consumption of well-/over-cooked red meat is associated with increased risk of BC.

Fish. n-3 polyunsaturated fatty acids (n-3 PUFA) have been described to inhibit or curtail carcinogenesis and reduce risk in animal models (20, 21), as well as *in vitro* cell studies (22); however, evidence in humans is inconclusive. According to prospective cohort studies, including the Singapore Chinese Health Study (35,298 Singapore Chinese women aged 45-74 years) (23) and the Japan Collaborative Cohort Study (26,291 women aged 40-79 years) (24), dietary n-3 PUFA are inversely associated with risk of BC. A recent meta-analysis demonstrated that higher consumption of dietary marine n-3 PUFA is associated with a 14% reduction of the risk of BC, whereas no significant association was observed for fish intake (25).

Conclusion: n-3 PUFA may be protective against the risk of BC.

Carbohydrate and Glycaemic Index

Available data about the association between carbohydrate intake, glycaemic index and glycaemic load and BC are inconclusive with some studies failing to show a strong association (26-29) and other studies suggesting that high carbohydrate intake and diets with high glycaemic index and glycaemic load may increase the risk of developing oestrogen receptor (ER)+/progesteron receptor (PR)3- BC (30) or BC in pre-menopausal women (31). In a recent large, population-based study that included both pre- and post-menopausal women (1,463 breast cancer cases and 1,500 controls), increasing overall intake of nutrients involved in glycaemic control was associated with decrease in BC risk (32). The role of glycaemic control in cancer development is gaining attention (33-36). Dietary carbohydrates tend to determine chronic hyperinsulinemia, which is associated with increased levels of insulin-like growth factor-1 (IGF-1) (37). In a large case-control study nested within the prospective Nurses' Health Study, involving 800 women with a diagnosis of invasive or *in situ* breast cancer, matched to a total of 1,129 controls, elevated serum levels of IGF-1 have been reported to be associated with BC (38). The possible mechanisms of this association is that insulin enhances growth hormone (GH)-stimulated IGF-1 synthesis (37), which is responsible for tumour development by increasing cell proliferation and inhibiting apoptosis (39). However, several nutrients might play a role in controlling insulin levels (37), including fibre, which reduces insulin response by slowing the absorption of glucose into the small intestine or calcium, magnesium and zinc that are involved with insulin secretion (40-42). In a multicenter Italian study, women were recruited from 1993 to 1998 at five centres and completed validated food frequency questionnaires. During 11 years of follow-up, 879 breast cancer (797 invasive and 82 *in situ*) cases were indentified and high dietary glycaemic load was associated with increased breast cancer risk (43).

Conclusion: Glycaemic control is advisable and appears to be associated to decreased risk of BC. There is a need to analyse multiple nutrient pathways rather than single nutrients and their effect on insulin secretion.

Fat and Cholesterol

High-fat diet has long been considered as an important aetiological factor in the development of BC (44). Initial suspicion that dietary fat may contribute to BC came from animal studies (45). This was confirmed in large epidemiological studies with estimates of a 2.5-fold risk reduction for BC if fat intake was reduced by 50% (46).

While a meta-analysis (47) and a prospective study in a US cohort comprising 188,736 post-menopausal women (48) showed an association between BC and overall fat consumption, irrespective of it being saturated or unsaturated, some others point towards an association with consumption of saturated fat only (49), although a recent meta-analysis shows no association (50). Associations were shown for both pre- and post-menopausal patient women (28, 51, 52) and the suggested mechanisms especially in post-menopausal women were related to the direct proportionality of fat consumption and adipose tissue, which can produce oestrogens and drive certain BCs (53). Furthermore, accumulated adipose tissue may lead to metabolic syndrome and tumourogenesis via pathways involving insulin and IGF-1 (54).

A case-control study conducted in India, involving 54 untreated breast cancer patients of different clinical stages and 42 age- and sex-matched controls, revealed that the plasma total cholesterol and the triglyceride levels were significantly elevated among BC patients as compared to the controls (55). Recently Franky *et al*. analysed plasma lipids from 70 controls, 30 patients with benign breast disease, 125 untreated breast cancer patients and 93 post-treatment follow-up samples and found that higher levels of very-low-density lipoprotein and triglycerides were significantly associated with increased breast cancer risk (56). Owiredu *et al*. included 100 breast cancer patients and 100 controls with similar age range (25 to 80 years) and found that dyslipidaemia and body mass index were associated with increased BC risk (57). A further study conducted in Egypt and Libya, including 119 breast cancer patients (60 pre-menopausal, 59 post-menopausal) and 50 control women (30 pre-menopausal women, 20 post-menopausal women) described differences according to hormonal status and found significantly higher mean total cholesterol levels in pre-menopausal patients, whereas mean triglycerides level were found to be significantly higher among post-menopausal patients (58). Previous findings have been confirmed in a recent Indian study including 160 women with a histologically proven diagnosis of BC, where a strong association of total cholesterol and triglyceride levels with BC in the Indian population was found (59). Most studies have suggested that higher saturated fat intake pre-diagnosis was associated with increased risk of BC–specific and all-cause mortality, whereas omega-3 fat intake suggested an inverse association with all-cause mortality in a recent systematic review (60). Recently, Sieri *et al*. prospectively evaluated fat intake as predictor of developing BC subtypes in a large (n=337,327) heterogeneous cohort of women, with 10,062 developing BC after 11.5 years median follow-up. They showed that high saturated fat intake in particular increases the risk of receptor-positive disease (61).

Conclusion: High-fat diet, total cholesterol and triglyceride levels are associated with increased risk of BC, although the impact of consumption of fat subtypes on BC recurrence and mortality is complex.

Polyphenols and Phyto-oestrogens

Polyphenols are secondary metabolites present in plant foods and they are divided into four main classes: flavonoids (anthocyanidins, flavonols, flavanones, flavones, flavanols and isoflavones), phenolic acids, stilbenes and lignans. There is evidence that polyphenols may exert anti-oxidant, anti-inflammatory and anti-carcinogenic properties (62, 63). Furthermore, in view of their weak oestrogen-like activity, phyto-oestrogens might interact with ERs in the development of BC (64). According to a recent meta-analysis, the intake of flavones and flavonols was found to be associated with a decreased risk of BC (65) but evidence from prospective cohort studies remains controversial (66-71). A recent meta-analysis (72) showed a significantly inverse association between isoflavones and BC risk in certain Asian countries, particularly in post-menopausal women, whereas no association has been described in Western countries. On the other hand, inconclusive results have been found for lignans (73, 74). In the French post-menopausal European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, including 58,049 post-menopausal French women who were not taking soy isoflavone supplements, dietary lignan intake was found to be protective against ER- and PR- tumours (75). In the Swedish EPIC cohort, which involved 366 cases and 733 matched controls, an inverse association between the plasma enterolactone concentration, a lignan intake biomarker and BC risk in ERa positive tumours, particularly in case of concomitant ERb negative was observed (76). In the Danish EPIC cohort that included 29,785 women, the same association was limited only to ER-negative tumours (77) and no association between BC and intake of both lignans and isoflavones was described in the Norfolk EPIC Study (78).

A recent study (79), which included 334,850 women, aged between 35 and 70 years from ten European countries, evaluated the association of dietary intake of flavonoids and lignans and risk of BC, according to menopause and hormone receptor status, within the EPIC Study (80). Zamora-Ros did not observe any association between total flavonoid, total lignan and flavonoid subclass intake and overall pre- and post-menopausal BC risk. No difference was shown when differentiating BC cases according to oestrogen and PRs (79).

Epidemiological studies found that the incidence of BC was lower in Asian women and this was associated to their high consumption of phyto-oestrogens found in high concentrations in foods, such as soy (81). Other sources of plant-derived oestrogens include flaxseed, cereals, grains, tea and berries. Food processing, such as boiling, has been shown to affect the concentration of phyto-oestrogens in food (82). Phyto-oestrogens are metabolized by the intestinal microflora into weakly oestrogenic compounds (81) and their availability can be affected by factors, such as genetic polymorphisms, use of antibiotics, gut transit times and types of food consumed, *e.g.* fibre intake has been shown to correlate positively (83). They have the ability to modulate protein transcription and gene expression in various organs (84). Structurally, they are similar to endogenous human oestrogens and they are either thought to prevent carcinogenesis by blocking oestroegen receptors on tumours or promoting oncogenesis by mimicking the action of oestrogens. There have been concerns that they even increase the risk or stimulate the growth of existing tumours (82).

Three meta-analyses published between 2006 and 2011 found that high soy intake was modestly associated with reduced BC risk in Asian but not in Western populations (72, 85, 86) and only few studies have analyzed this association in Western populations (87). A further meta-analysis reported no association between soy intake and BC in Asian countries (88). Furthermore, the four studies reported conflicting results when differentiating according to hormonal status; Trock *et al.* (88) and Qin *et al.* (85) reported that the protective effects were more evident in pre-menopausal than post-menopausal women, whereas Dong (72) reported that the effects were stronger in post-menopausal subgroup. Wu *et al.* described a dose-response relationship between soy intake and BC risk for doses greater or equal to 20 mg of isoflavones (86). In a systematic review, de Lemos showed that low levels of phyto-oestrogens will stimulate oestrogen receptor positive tumours, while higher levels will inhibit (89). However, such high levels of phyto-oestrogens (>10 μmol/l) are difficult to achieve through diet (90). A recent prospective Japanese study, including 15,607 women aged 35 years or older, reported that dietary soy and isoflavone intake had significant inverse associations with the risk of only post-menopausal BC, with no effect in pre-menopausal BC (91). Anderson *et al.* investigated the association between phyto-oestrogen intake from foods during both adolescence and adulthood and BC risk according to receptor tumour sub-groups among women in The Ontario Women's Diet and Health Study (OWDHS), a population-based case–control study which included 3,101 cases and 3,471 controls. They found a minimal to null association between BC risk and phyto-oestrogen intake during adulthood, independent of hormone receptor status. High lignan intake was associated with reduced BC risk across all ERPR subgroups for all women and post-menopausal women, although statistical significance was not reached. When considering phyto-oestrogen intake during adolescence, a significant association with decreased post-menopausal BC risk was observed, mainly for ER^+PR^+ tumours (92). A recent population-based case-control study in German post-menopausal women, including 2,884 cases and 5,509 controls, found a reduced post-menopausal BC risk when consuming a diet rich in sunflower or pumpkin seeds and soybeans (93).

Fritz *et al.* conducted a systematic review of soy and red clover for the potential impact on risk of BC incidence or recurrence and found that soy consumption may be associated

with reduced risk of BC incidence, recurrence and mortality, although further studies are needed prior to suggest high-dose (≥100 mg) consumption of isoflavones for BC patients (94).

Conclusion: There is evidence to support a possible protective role for polyphenols in reducing BC risk. Available studies suggest an inverse association between phyto-oestrogen consumption and BC risk, although only few studies investigated this association in Western populations.

Fruits and Vegetables

Fruits and vegetables have been described to have a protective role in distinct cancer types including BC, partially due to their high content of polyphenols and fibres (95, 96). A large cohort study, including 350 post-menopausal and 257 pre-menopausal women, showed an inverse relationship between fibre intake and BC (97). Other studies failed to draw such strong associations (98, 99). In a recent meta-analysis, Suzuki *et al*. estimated a risk reduction of 34% for women with a high fibre intake derived from fruit sources (100). Fibre is thought to interact with the entero-hepatic circulation and hence affect steroid and oestrogen metabolism. Finally, fibre may prevent carcinogenesis by improving insulin sensitivity and counteracting weight gain.

Jung *et al*. followed 993,466 women for 11 to 20 years in 20 cohort studies, documented 19,869 oestrogen receptor positive (ER(+) and 4821 ER(–) breast cancers. They found evidence that higher intake of total fruits and vegetables is associated with a lower risk of ER- but not ER+ BC (101). Similar findings have been reported previously (102). Furthermore, in recent pooled analyses of dietary carotenoids (103) or blood carotenoid measurements (104), inverse associations were also much stronger for ER- BC. In a recent prospective study, Fung *et al*. examined associations between 29 different types of fruits and vegetables and risk of ER- BC among post-menopausal women (75,929 women aged 38-63 years at baseline and followed for up to 24 years) (105) and they found an inverse association between ER- BC and intakes of blueberries, which are rich in anti-oxidants and polyphenols (106), strawberries and peaches/nectarines.

In the Italian section of the EPIC study, over 31,000 women, aged 36-64 years, recruited in five Italian centres between 1993 and 1998, were available for analyses with dietary and lifestyle information and anthropometric measurements. After a median follow-up of 11.25 years, 1,072 invasive and *in situ* incident BC cases were identified. An inverse association between consumption of all vegetables and BC risk was found (mainly leafy, fruiting vegetables and raw tomato), whilst no association of fruit with BC risk was found (107). Among the possible anti-tumor mechanisms involved, fruits and vegetables may reduce BC risk due to anti-oxidant effect (108). In some studies, strawberry and blueberry extracts have been found to reduce growth in BC cell lines (109, 110). Moreover, in animal studies, strawberries' extract was described to slow-down tumor progression by enhancing apoptosis (111). Additionally, peaches' extract may reduce proliferation in oestrogen-independent BC cell lines (112).

Conclusion: There is evidence to support a protective role for fruits and vegetables against BC, although results may differ according to hormonal status.

Lycopenes

Lycopene is a carotenoid pigment and phytochemical found in tomatoes and other red fruits and vegetables, such as red carrots, watermelons and papayas (but not strawberries, red bell peppers or cherries). There is increasing interest in the protective effect of dietary carotenoid intake on the risk of BC originating from the inhibitory effects of lycopene on BC cell lines (113-115). The protective role of lycopene against BC had been reported in the 1990's. Dorgan *et al*. conducted a case-control study nested in a cohort from the Breast Cancer Serum Bank in Columbia, Missouri (United States). During up to 9.5 years of follow-up (1977-1987), 105 cases of histologically confirmed BC were diagnosed. For each case, two matched women were selected as controls. Serum lycopene also was associated inversely with risk and, among women who donated blood at least two years before diagnosis, a significant gradient of decreasing BC risk with increasing lycopene concentration was evident (116).

Eliassen studied a pooled analysis of eight cohort studies comprising more than 80% of the world's published prospective data on plasma or serum carotenoids and BC (3,055 BC and 3,956 matched control subjects). Lycopene was reported to be statistically significantly inversely associated with BC risk (104). In contrast, the study by Kabat *et al*. analyzed baseline and repeated serum measurements of carotenoids, retinol and tocopherols to assess their associations with post-menopausal BC risk. Of 5,450 women with baseline measurements, 190 incident cases of BC were ascertained over a median of 8.0 years of follow-up. They reported that risk of invasive BC was inversely associated with baseline serum α-carotene concentrations and positively associated with baseline lycopene, although this positive association was not confirmed by time-dependent analyses (117).The meta-analysis by Hu *et al*. included 6 cohort studies and 9 case–control studies on the relationship between lycopene and BC. Comparing the highest with the lowest intake, dietary intake of lycopene did not significantly reduce the BC risk when data from cohort studies were pooled; however, when data from case–control studies were pooled, dietary intake of lycopene significantly (p=0.01) reduced the BC risk by 29.0% (118).

BC risk among post-menopausal women increases as body mass index increases and studies have investigated the effects of carotenoids and isoflavones on circulating adipokines in post-menopausal women. Llanos *et al*., in their longitudinal

crossover trial, recruited seventy post-menopausal women at increased BC risk. All the participants underwent a 10-week period of consumption of a tomato-based diet (≥25 mg lycopene daily) and a further 10-week period of consumption of a soy-based diet (≥40 g of soy protein daily) with a 2-week washout in-between. They showed that phytonutrients, found in tomatoes, may act as BC preventive agents as increasing dietary consumption of tomato-based foods may beneficially increase serum adiponectin concentrations. The benefit was amongst post-menopausal women at increased BC risk, especially those who were not obese (119).

In a recent Chinese case-control study, 561 BC cases and 561 control cases were recruited and dietary intake information was collected by a face-to-face interview. An inverse association was observed between the consumption of α-carotene, β-carotene, β-cryptoxanthin and lutein/zeaxanthin and the risk of BC (all subtypes of hormone receptor status), particularly among pre-menopausal women and women who were exposed to second-hand smoke (120).

Tamini *et al*. conducted a prospective nested case-control study consisting of 604 BC cases and 626 controls and assessed whether the association between carotenoids and BC risk varies by mammographic density, which is known as one of the strongest predictors of breast cancer risk. They reported that mammographic density significantly modified the association between total circulating carotenoids and BC and circulating total carotenoids were inversely associated with BC risk (p trend=0.01). Moreover, among women with the highest tertile of mammographic density, total carotenoids were associated with a 50% reduction in BC risk (121).

As insulin-like growth factor-1 (IGF-1) is an important growth factor associated with increased risk of pre-menopausal BC, a recent randomized, placebo-controlled, double-blind, crossover trial, evaluated whether tomato-derived lycopene supplementation (30 mg/day for 2 months) decreases serum levels of total IGF-1 in pre-menopausal women with a history of BC (n=24) or a high familial BC risk (n=36). Two months of lycopene supplementation was reported to have no effect on serum total IGF-1 in the overall study population but the results were discordant between the two study populations showing beneficial effects in high-risk healthy women but not in BC survivors (122).

Conclusion: There is evidence to suggest benefit of lycopene, especially in those with low dietary intake or low blood levels.

Vitamins and Oligo-elements

Vitamin D & Calcium. Vitamin D has been found to have potential anti-carcinogenic properties including regulation of apoptosis, cell differentiation, cell growth and growth factor signalling (123). Both epidemiological and experimental data suggest an inverse association between vitamin D and BC (124-126). Furthermore, epidemiological studies have shown an inverse association between sun exposure and incidence of BC (127). Larger cohort and randomized-control studies have shown a risk reduction of up to 45% with high endogenous levels (128) or higher daily supplemented dose of vitamin D at >400 IU (129) or >1100 IU (130). Subsequently, Anderson *et al*. were able to show in a case-control study, including 3,101 cases and 3,471 controls, that vitamin D from supplements was independently associated with reduced BC risk (131). However, a recent systematic review failed to show a conclusive association between vitamin D and BC (132). Abbas *et al*. recently investigated the association between dietary vitamin D and calcium intake from foods and BC risk in a heterogeneous population (7,760 incident invasive BC cases identified among 319,985 women) from different countries in Europe within the EPIC study and they did not find any significant association (133).

Plasma 25(OH)D is the precursor of the active hormone 1,25(OH)2 vitamin D and the most commonly used vitamin D status marker. Results from prospective studies on a relationship between 25(OH)D levels and BC risk have been inconclusive (134-138). Kuhn and co-workers prospectively investigated the relationship between 25(OH)D levels and BC risk in a larger EPIC-wide prospective case–control study (1,391 incident BC cases and 1,391 controls) and they did not find a prospective association between 25(OH)D levels and the risk of BC, independently on ER and PR status, menopausal status, age or time between blood donation and BC diagnosis (139). In a recent meta-analysis, including 9 prospective studies, Bauer *et al*. focused on the relationship between circulating 25(OH)D and BC risk according to menopausal status. No association was found in pre-menopausal women, whereas in post-menopausal women an inverse association was observed beyond a threshold of 27 ng/ml, but with flattening of effects above 35 ng/ml (140). Given an US average circulating 25(OH)D level of 24 ng/ml, daily supplementation of 1,000 IU/d vitamin D would be needed to reach the approximate threshold of 35 ng/ml (141).

Sperati *et al*., in their systematic review, specifically analysed randomized clinical trials focused on vitamin D supplementation in BC prevention (142, 143) and reported that vitamin D supplementation was not associated with a reduced risk of BC development in post-menopausal women, although the available data are limited to draw firm conclusions (144).

However, most recently, Li *et al*., in their meta-analysis showed that higher 25(OH)D levels, at or near the time of diagnosis, were significantly associated with improved disease-free survival for patients with BC ($p<0.001$) (145). These results have been recently confirmed by Kim and co-workers who reported that high 25(OH)D levels were weakly associated with low BC risk but strongly associated with better BC survival (146).

With regards to calcium, there is less scientific evidence that it might exert anti-carcinogenic action, although effects of calcium on cell proliferation and apoptosis have been reported (147). Intake of calcium has been shown to lower incidence of BC in a recent meta-analysis (128) and this has been demonstrated for doses between 780 and 1,750 mg and primarily in pre-menopausal women only (132). A large randomized control study including 36,282 post-menopausal women failed to show any significant risk reduction of invasive BC in post-menopausal women (148). There is evidence to support that women who had BC also have low levels of vitamin D and calcium. This might be associated with disease carcinogenesis and recurrence (149).

Conclusion: There is evidence that vitamin D, and less evidence that calcium, decreases BC risk. The benefit of vitamin D supplementation for post-menopausal women is currently being assessed in on-going VITAL trial (VITamin D and megA-3 TriaL (VITAL) website; http://www.vitalstudy.org/).

Zinc and Beta-carotene, Folate and Vitamins (A, B, C, E). The possible onco-protective properties of these micronutrients have been attributed to their anti-oxidative properties. Many studies failed to show conclusive results (150, 151).

Zinc is a trace mineral, which is known to be essential for cell proliferation and important for tumour growth (152). Moreover, zinc is known to be a regulator of immunity. In vivo, zinc deficiency alters the number and function of neutrophils granulocytes, monocytes, natural killer cells, T- and B-cells. Particularly, T cell functions and balance between the different subsets are particularly susceptible to changes in zinc status (153).

In a recent study, which included 2,362 BC cases (866 pre-menopausal and 1,496 post-menopausal) and 2,462 controls, supplementations of 10 years or longer of multiple vitamins, beta-carotene, vitamin C, vitamin E and zinc were associated with statistically significant reductions for BC risk in post-menopausal women (154). A recent pooled analysis of eight prospective studies (104) observed a statistically significant inverse associations between circulating levels of individual and total carotenoids and BC risk. Inverse associations were observed for α-carotene, β-carotene, lutein plus zeaxanthin and lycopene, but not β-cryptoxanthin. Associations were generally found to be stronger among lean women and for ER−tumours and, for lutein plus zeaxanthin and total carotenoids, associations were stronger among current smokers.

Dietary and supplemental sources of vitamin E compounds might influence critical pathways involved in cancer. Vitamin E occurs naturally in eight isoforms of α-, β-, γ- and δ-tocopherols or tocotrienols (T3). T3 are mainly present in palm, rice and annatto. Pierpaoli and co-workers investigated the effect of dietary supplementation with T3 extracts from annatto seeds n the development of mammary tumours in *HER-2/neu* transgenic mice and observed that annatto-T3 may exert important anti-tumour effects delaying the development and the metastasizing capacity of tumours in mice transgenic for the *HER-2/neu* oncogene (155). Tocotrienols have been reported to exert potent anti-proliferative effects on human BC cells (156). Recently, Loganathan *et al*. compared anti-malignant effects of pure vitamin E analogues (tocotrienol analogues (α, δ and γ) and α tocopherol), a tocotrienol-rich fraction (TRF) and a tocotrienol enriched fraction (TEF) isolated from palm oil on two human breast cancer cell lines and they found a marked induction of apoptosis in both cell lines by tocotrienols compared to treatment with paclitaxel, which was used as positive control (157). In view of their findings, palm tocotrienols seem to induce apoptosis in human BC cells, through specific genetic pathways.

One-carbon metabolism comprises a complex network of biochemical pathways and involves interactions between several B vitamins, homocysteine and methionine. Dietary methyl groups are mainly derived from folate, methionine and riboflavin, vitamin B6 and vitamin *B12* are important co-factors in the one-carbon metabolism. Any disregulation in the one-carbon metabolism may affect DNA replication, DNA repair and regulation of gene expression through methylation, which are all key factors in tumour promotion (158), therefore dietary intake of B vitamins and methionine might play an important role in carcinogenesis. According to two recent meta-analyses, no evidence of an association between BC risk and dietary folate intake was observed in prospective studies, whereas an inverse association was found for case–control studies (159, 160). Null findings for overall BC risk and vitamin B6, vitamin B12, riboflavin and methionine have been reported in the majority of studies so far (161-163). Other factors might influence the associations between B vitamin and methionine intake and BC risk, including dietary folate intake (162). In a recent prospective study with a follow-up of 20,756 women from the Melbourne Collaborative Cohort Study for an average of 16 years and 936 incident BC, Bassett *et al*. investigated the relationship between dietary intakes of methionine and B vitamins associated with one-carbon metabolism and BC risk and they reported a weak inverse association between BC risk and riboflavin intake and a weak positive association for vitamin B12 (164). Furthermore, there was some evidence that high methionine intake might be protective against BC in women with high folate intakes (164). Yang *et al*. in their case-control study, including 2,325 cases and 2,525 controls, found that folate and B-vitamin intake might influence BC risk, but that folate intake seems to be related specifically to risk for the ER-phenotype (165). A recent case-control study found a significant association between *MTHFR* C667T polymorphism, folate intake (<450 μg/day) and vitamin B6 (<0.84 mg/day) and increased BC risk, suggesting that folate and other methyl-related B vitamins have a role in developing BC (166). These findings are consistent

Table I. *Summary of current evidence regarding the association between dietary factors and risk of breast cancer.*

Key points
Dietary factors may play an important role in breast cancer.
Red meat intake and dietary sugar should be reduced, whereas increased fish intake appears to be protective
Fruit and vegetables, as well as nutritional supplements, including poly-phenols, have shown promising results but further randomized studies are warranted to confirm these finding.
Alcohol is a risk factor for breast cancer and intake should be minimised, since it is a risk factor for breast cancer.
Prospective randomized trials are needed to develop population-based prevention strategies for breast cancer; however, they are difficult to design due to many variable factors, *e.g.* lifestyle, nutritional body mass and ethnicity.

with two previous studies reporting that high intake of vitamin B6 had an association with a decreased risk of BC in Chinese and Brazilian female populations (163, 167), although Lin *et al*. conducted a case-control study with 848 cases and 848 controls and reported no association between folate, vitamin B6, vitamin B12 intake and overall BC risk (168). However, the inconsistency of these studies may be induced by differences in ethnicities, control subjects, sample size.

Conclusion: There is evidence that zinc and to a lesser extent vitamin E and B might decrease BC risk through their anti-oxidant properties and interaction with pathways involved in carcinogenesis.

Alcohol

The association between alcohol and BC has been firmly established in the last four decades (169-171). In their pooled analysis of six prospective studies, Smith-Warner *et al*. suggested that there is a 7% increased risk of BC with every 10 g of alcohol consumed per day (170). The mechanism of action may involve appetite disinhibition and weight gain, as well as potentiation of oestrogen action (172). Another suggested mechanism might involve folate metabolism. Alcohol is a known folate antagonist, which may impair folate absorption and metabolism (173).Thus adequate folate intake might attenuate the increased risk of BC due to alcohol consumption (159). A recent Chinese case-control study, which included 669 cases and 682 population-based controls, confirmed previous findings, suggesting that alcohol intake may represent a risk factor for BC. Interestingly, the same study found a significant positive relationship between BC risk and the degree of husbands' smoking (*i.e*. passive smoking) (174).

A recent study, including 66,481 women from the French E3N-EPIC cohort who were followed-up and asked to report their alcohol consumption, by type of alcohol, through a 208-item diet-history questionnaire, reported a total of 2,812 BC cases and a linear association between total alcohol consumption and BC risk was found only in the subgroup of post-menopausal women, particularly for wine and beer consumption and for ER+/PR+ BC subtypes. Additionally, higher increased risks were observed for high alcohol intake among women with low folate intake or who were overweight or obese (175).

Conclusion: Alcohol intake is a risk factor for BC occurrence and should be minimized. However, interactions between type of alcohol and other factors *e.g*. obesity, ER and PR status needs to be better understood.

Conclusion

Epidemiological and pre-clinical studies have suggested that dietary factors may play an important role in BC. However available data can often be inconclusive.

In our review, we set out to identify nutritional factors that might play a role in the development of BC (Table I). Consumption of well-done red meat appears to be associated with increased risk of BC, whereas n-3 PUFA in fish might exert a protective role. High total cholesterol and triglyceride levels seem to be associated with increased risk of BC, although further prospective studies are required with a focus on the impact of consumption of fat subtypes on BC recurrence and mortality. Glycaemic load should be monitored and controlled in at risk populations because it might be associated with increased risk of BC, although the exact mechanism has yet to be fully elucidated. Alcohol intake should be minimised, since available data suggest that it is a risk factor for BC. There is evidence that high intake of polyphenol/phyto-oestrogen -rich food (*i.e*. flavonoids, soya products), as well as fibres, fruits and vegetables, may have a protective effect against BC occurrence, but results are still inconclusive and might be different according to hormonal status. Vitamin D supplements might be beneficial to protect against BC development, although supplementation for post-menopausal women is currently being validated in a large clinical trial. Other vitamins and oligo-elements might decrease BC risk through their anti-oxidant properties and their interaction with pathways involved in carcinogenesis.

In heterogeneous populations with different lifestyle, nutritional body mass index and many other variables it is difficult to design prospective randomized trials to develop population-based prevention strategies for BC.

Conflict of Interest

The Authors declare no conflicts of interest.

References

1 Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. CA Cancer J Clin *61*: 69-69, 2011.

2 http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-031941.pdf Am. Cancer Soc. (2012). Cancer Facts &Figures 2012. Atlanta, GA: Am. Cancer Soc.

3 http://www.cancer.org/Cancer/BreastCancer/OverviewGuide/breast-cancer-overview-survival-rates Am. Cancer Soc. (2011). Survival Rates for Breast Cancer. Atlanta, GA: Am. Cancer Soc.

4 Zare N, Haem E, Lankarani KB, Heydari ST and Barooti E: Breast cancer risk factors in a defined population: weighted logistic regression approach for rare events. J Breast Cancer *16*: 214-219, 2013.

5 Rose DP and Vona-Davis L: Biochemical and molecular mechanisms for the association between obesity, chronic Inflammation, and breast cancer. Biofactors *40*: 1-12, 2014.

6 McCullough ML and Giovannucci EL: Diet and cancer prevention. Oncogene *23*: 6349-6364, 2004.

7 World Cancer Res. Fund Int./Am. Inst. Cancer Res. (2010). Continuous Update Project ReportSummary. Food, Nutrition, Physical Activity, and the Prevention of Breast Cancer. London:World Cancer Res. Fund Int. http://www.dietandcancerreport.org/cancer_resource_center/cup_summaries.php

8 Tappel A: Heme of consumed red meat can act as a catalyst of oxidative damage and could initiate colon, breast and prostate cancers, heart disease and other diseases. Med Hypotheses *68*: 562-564, 2007.

9 Ito N, Hasegawa R, Sano S, Tamano S, Esumi H, Takayama S and Sugimura T: A new colon and mammary carcinogen in cooked food, 2-amino-1-methyl-6-phenylimidazo[4,5b]pyridine (PhIP). Carcinogenesis *12*: 1503-1506, 1991.

10 Zheng W, Gustafson DR, Sinha R, Cerhan JR, Moore D, Hong CP, Anderson KE, Kushi LH, Sellers TA and Folsom AR: Well-done meat intake and the risk of breast cancer. J Natl Cancer Inst *90*: 1724-1729, 1998.

11 Kushi LH, Sellers TA, Potter JD, Nelson CL, Munger RG, Kaye SA, Folsom AR: Dietary fat and postmenopausal breast cancer. J Natl Cancer Inst *84*: 1092-1099, 1992.

12 Knekt P, Steineck G, Jarvinen R, Hakulinen T and Aromaa A: Intake of fried meat and risk of cancer: a follow-up study in Finland. Int J Cancer *59*: 756-760, 1994.

13 De Stefani E, Ronco A, Mendilaharsu M, Guidobono M and Deneo-Pellegrini H: Meat intake, heterocyclic amines, and risk of breast cancer: a case-control study in Uruguay. Cancer Epidemiol Biomarkers Prev *6*: 573-578, 1997.

14 Ceccatto V, Cesa C, Kunradi Vieira FG, Altenburg de Assis MA, Crippa CG and Faria Di Pietro P: Characteristics of newly diagnosed women with breast cancer: a comparison with the recommendations of the WCRF/AICR Second Report. Nutr Hosp *27*: 1973-1980, 2012.

15 Qureshi SA, Couto E, Hofvind S, Wu AH and Ursin G: Alcohol intake and mammographic density in postmenopausal Norwegian women. Breast Cancer Res Treat *131*: 993-1002, 2012.

16 Alexander DD, Morimoto LM, Mink PJ and Cushing CA: A review and eta-analysis of red and processed meat consumption and breast cancer. Nutr Res Rev *23*: 349-365, 2010.

17 Nowell SA, Ahn J and Ambrosone CB: Gene-nutrient interactions in cancer etiology. Nutr Rev *62*: 427-438, 2004.

18 Taylor VH, Misra M and Mukherjee SD: Is red meat intake a risk factor for breast cancer among premenopausal women? Breast Cancer Res Treat *117*: 1-8, 2009.

19 Farvid MS, Cho E, Chen WY, Eliassen AH and Willett WC: Dietary protein sources in early adulthood and breast cancer incidence: prospective cohort study. BMJ *348*: g3437, 2014.

20 Karmali RA, Marsh J and Fuchs C: Effect of omega-3 fatty acids on growth of a rat mammary tumor. J Natl Cancer Inst *73*: 457-461, 1984.

21 Kort WJ, Weijma IM, Bijma AM, van Schalkwijk WP, Vergroesen AJ and Westbroek DL: Omega-3 fatty acids inhibiting the growth of a transplantable rat mammary adenocarcinoma. J Natl Cancer Inst *79*: 593-599, 1987.

22 Schley PD, Jijon HB, Robinson LE and Field CJ: Mechanisms of omega-3 fatty acid-induced growth inhibition in MDA-MB-231 human breast cancer cells. Breast Cancer Res Treat *92*: 187-195, 2005.

23 Gago-Dominguez M, Yuan JM, Sun CL, Lee HP and Yu MC: Opposing effects of dietary n-3 and n-6 fatty acids on mammary carcinogenesis: the Singapore Chinese Health Study. Br J Cancer *89*: 1686-1692, 2003.

24 Wakai K, Tamakoshi K, Date C, Fukui M, Suzuki S, Lin Y, Niwa Y, Nishio K, Yatsuya H, Kondo T, Tokudome S, Yamamoto A, Toyoshima H and Tamakoshi A; JACC Study Group: Dietary intakes of fat and fatty acids and risk of breast cancer: a prospective study in Japan. Cancer Sci *96*: 590-599, 2005.

25 Zheng JS, Hu XJ, Zhao YM, Yang J and Li D: Intake of fish and marine n-3 polyunsaturated fatty acids and risk of breast cancer: meta-analysis of data from 21 independent prospective cohort studies. BMJ *346*: f3706, 2013.

26 Cho E, Spiegelman D, Hunter DJ, Chen WY, Colditz GA and Willett WC: Premenopausal dietary carbohydrate, glycemic index, glycemic load, and fiber in relation to risk of breast cancer. Cancer Epidemiol Biomarkers Prev *12(11 Pt 1)*: 1153-1158, 2003.

27 Higginbotham S, Zhang ZF, Lee IM, Cook NR, Buring JE and Liu S: Dietary glycemic load and breast cancer risk in the Women's Health Study. Cancer Epidemiol Biomarkers Prev *13*: 65-70, 2004.

28 Sieri S, Krogh V, Ferrari P, Berrino F, Pala V, Thiébaut AC, Tjønneland A, Olsen A, Overvad K, Jakobsen MU, Clavel-Chapelon F, Chajes V, Boutron-Ruault MC, Kaaks R, Linseisen J, Boeing H, Nöthlings U, Trichopoulou A, Naska A, Lagiou P, Panico S, Palli D, Vineis P, Tumino R, Lund E, Kumle M, Skeie G, González CA, Ardanaz E, Amiano P, Tormo MJ, Martínez-García C, Quirós JR, Berglund G, Gullberg B, Hallmans G, Lenner P, Bueno-de-Mesquita HB, van Duijnhoven FJ, Peeters PH, van Gils CH, Key TJ, Crowe FL, Bingham S, Khaw KT, Rinaldi S, Slimani N, Jenab M, Norat T and Riboli E: Dietary fat and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition. Am J Clin Nutr *88*: 1304-1312, 2008.

29 George SM, Mayne ST, Leitzmann MF, Park Y, Schatzkin A, Flood A, Hollenbeck A and Subar AF: Dietary glycemic index, glycemic load, and risk of cancer: a prospective cohort study. Am J Epidemiol *169*: 462-472, 2009.

30 Larsson SC, Bergkvist L and Wolk A: Glycemic load, glycemic index and breast cancer risk in a prospective cohort of Swedish women. Int J Cancer *125*: 153-157, 2009.

31 Wen W, Shu XO, Li H, Yang G, Ji BT, Cai H, Gao YT and Zheng W: Dietary carbohydrates, fiber, and breast cancer risk in Chinese women. Am J Clin Nutr *89*: 283-289, 2009.

32 Bradshaw PT, Khankari NK, Teitelbaum SL, Xu X, Fink BN, Steck SE, Gaudet MM, Kabat GC, Wolff MS, Neugut AI, Chen J and Gammon MD: Nutrient pathways and breast cancer risk: the Long Island Breast Cancer Study Project. Nutr Cancer *65*: 345-354, 2013.

33 Coulston AM, Hollenbeck CB, Swislocki AL and Reaven GM: Effect of source of dietary carbohydrate on plasma glucose and insulin responses to mixed meals in subjects with NIDDM. Diabetes Care *10*: 395-400, 1987.

34 Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, Mitchell P and Brand-Miller JC: Glycemic index, glycemic load, and chronic disease risk—a meta-analysis of observational studies. Am J Clin Nutr *87*: 627-637, 2008

35 Mulholland HG, Murray LJ, Cardwell CR and Cantwell MM: Dietary glycaemic index, glycaemic load and breast cancer risk: A systematic review and meta-analysis. Br J Cancer *99*: 1170-1175, 2008.

36 Shikany JM, ReddenDT, Neuhouser ML, Chlebowski RT, Rohan TE, Simon MS, Liu S, Lane DS and Tinker L: Dietary glycemic load, glycemic index, and carbohydrate and risk of breast cancer in the women's health initiative. Nutr Cancer *63*: 899-907, 2011.

37 Kaaks R and Lukanova A. Energy balance and cancer: The role of insulin and insulin-like growth factor-I. Proc Nutr Soc *60*: 91-106, 2001.

38 Schernhammer ES, Holly JM, Pollak MN, and Hankinson SE: Circulating levels of insulin-like growth factors, their binding proteins, and breast cancer risk. Cancer Epidemiol Biomarkers Prev *14*: 699-704, 2005.

39 Werner H and LeRoith D: The role of the insulin-like growth factor system in human cancer. Adv Cancer Res *68*: 183-223, 1996.

40 Paolisso G, Scheen A, D'Onofrio F and Lefvebre P: Magnesium and glucose homeostasis. Diabetologia *33*: 511-514, 1990.

41 Rungby J: Zinc, zinc transporters and diabetes. Diabetologia 53: 1549–1551, 2010

42 Rutter GA, Tsuboi T and Ravier MA: Ca^{2+} microdomains and the control of insulin secretion. Cell Calcium *40*: 539-551, 2006.

43 Sieri S, Pala V, Brighenti F, Agnoli C, Grioni S, Berrino F, Scazzina F, Palli D, Masala G, Vineis P, Sacerdote C, Tumino R, Giurdanella MC, Mattiello A, Panico S and Krogh V: High glycemic diet and breast cancer occurrence in the Italian EPIC cohort. Nutr Metab Cardiovasc Dis *23*: 628-634, 2013.

44 Hunter DJ and Willett WC: Diet, body size, and breast cancer. Epidemiol Rev *15*: 110-132, 1993.

45 Fay MP, Freedman LS, Clifford CK and Midthune DN: Effect of different types and amounts of fat on the development of mammary tumors in rodents: a review. Cancer Res *57*: 3979-3988, 1997.

46 Prentice RL and Sheppard L: Dietary fat and cancer: consistency of the epidemiologic data, and disease prevention that may follow from a practical reduction in fat consumption. Cancer Causes Control *1*: 81-97, 1990.

47 Boyd NF, Martin LJ, Noffel M, Lockwood GA and Trichler DL: A meta-analysis of studies of dietary fat and breast cancer risk. Br J Cancer *68*: 627-636, 1993.

48 Thiebaut AC, Kipnis V, Chang SC, Subar AF, Thompson FE, Rosenberg PS, Hollenbeck AR, Leitzmann M and Schatzkin A: Dietary fat and postmenopausal invasive breast cancer in the National Institutes of Health-AARP Diet and Health Study cohort. J Natl Cancer Inst *99*: 451-462, 2007.

49 Smith-Warner SA, Spiegelman D, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Kushi LH, Miller AB, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A and Hunter DJ: Types of dietary fat and breast cancer: a pooled analysis of cohort studies. Int J Cancer *92*: 767-774, 2001.

50 Alexander DD, Morimoto LM, Mink PJ and Lowe KA: Summary and meta-analysis of prospective studies of animal fat intake and breast cancer. Nutr Res Rev *23*: 169-179, 2010.

51 Prentice RL, Caan B, Chlebowski RT, Patterson R, Kuller LH, Ockene JK, Margolis KL, Limacher MC, Manson JE, Parker LM, Paskett E, Phillips L, Robbins J, Rossouw JE, Sarto GE, Shikany JM, Stefanick ML, Thomson CA, Van Horn L, Vitolins MZ, Wactawski-Wende J, Wallace RB, Wassertheil-Smoller S, Whitlock E, Yano K, Adams-Campbell L, Anderson GL, Assaf AR, Beresford SA, Black HR, Brunner RL, Brzyski RG, Ford L, Gass M, Hays J, Heber D, Heiss G, Hendrix SL, Hsia J, Hubbell FA, Jackson RD, Johnson KC, Kotchen JM, LaCroix AZ, Lane DS, Langer RD, Lasser NL and Henderson MM: Low-fat dietary pattern and risk of invasive breast cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA *295*: 629-642, 2006.

52 Wang J, John EM, Horn-Ross PL and Ingles SA: Dietary fat, cooking fat, and breast cancer risk in a multiethnic population. Nutr Cancer *60*: 492-504, 2008.

53 Sugimura T: Nutrition and dietary carcinogens. Carcinogenesis *21*: 387-395, 2000.

54 Blackburn GL and Wang KA: Dietary fat reduction and breast cancer outcome: results from the Women's Intervention Nutrition Study (WINS). Am J Clin Nutr *86*: s878-881, 2007.

55 Ray G and Husain SA: Role of lipids, lipoproteins and vitamins in women with breast cancer. Clin Biochem *34*: 71-76, 2001.

56 Franky Dhaval S, Shilin Nandubhai S, Pankaj Manubhai S, Patel HR and Prabhudas Shankerbhai Patel: Significance of alterations in plasma lipid profile levels in breast cancer. Integr Cancer Ther *7*: 33-41, 2008.

57 Owiredu WK, Donkor S, Addai BW and Amidu N: Serum lipid profile of breast cancer patients. Pak J Biol Sci *12*: 332-338, 2009.

58 Abu-Bedair FA, El-Gamal BA, Ibrahim NA and El-Aaser AA: Serum lipids and tissue DNA content in Egyptian female breast cancer patients. Jpn J Clin Oncol *33*: 278-282, 2003.

59 Kapil U, Bhadoria AS, Sareen N, Singh P and Dwivedi SN: Total cholesterol and triglyceride levels in patients with breast cancer. J Breast Cancer *16*: 129-130, 2013.

60 Makarem N, Chandran U, Bandera EV and Parekh N: Dietary fat in breast cancer survival. Annu Rev Nutr *33*: 319-348, 2013.

61 Sieri S, Chiodini P, Agnoli C, Pala V, Berrino F, Trichopoulou A, Benetou V, Vasilopoulou E, Sánchez MJ, Chirlaque MD, Amiano P, Quirós JR, Ardanaz E, Buckland G, Masala G, Panico S, Grioni S, Sacerdote C, Tumino R, Boutron-Ruault

MC, Clavel-Chapelon F, Fagherazzi G, Peeters PH, van Gils CH, Bueno-de-Mesquita HB, van Kranen HJ, Key TJ, Travis RC, Khaw KT, Wareham NJ, Kaaks R, Lukanova A, Boeing H, Schütze M, Sonestedt E, Wirfält E, Sund M, Andersson A, Chajes V, Rinaldi S, Romieu I, Weiderpass E, Skeie G, Dagrun E, Tjønneland A, Halkjær J, Overvard K, Merritt MA, Cox D, Riboli E and Krogh V: Dietary fat intake and development of specific breast cancer subtypes. J Natl Cancer Inst 106. pii: dju068. doi: 10.1093/jnci/dju068, 2014.

62 Cazarolli LH, Zanatta L, Alberton EH, Figueiredo MS, Folador P, Damazio RG, Pizzolatti MG and Silva FR: Flavonoids: prospective drug candidates. Mini Rev Med Chem *8*: 1429-1240, 2008.

63 Adolphe JL, Whiting SJ, Juurlink BH, Thorpe LU and Alcorn J: Health effects with consumption of the flax lignan secoisolariciresinol diglucoside. Br J Nutr *103*: 929-938, 2010.

64 Rice S and Whitehead SA: Phytoestrogens oestrogen synthesis and breast cancer. J Steroid Biochem Mol Biol *108*: 186-195, 2008.

65 Hui C, Qi X, Qianyong Z, Xiaoli P, Jundong Z and Mantian M: Flavonoids, flavonoid subclasses and breast cancer risk: a meta-analysis of epidemiologic studies. PLoS One *8*: e54318, 2013.

66 Knekt P, Jarvinen R, Seppanen R, Hellövaara M, Teppo L, Pukkala E and Aromaa A: Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. Am J Epidemiol *146*: 223–230, 1997.

67 Knekt P, Kumpulainen J, Jarvinen R, Rissanen H, Heliövaara M, Reunanen A, Hakulinen T and Aromaa A: Flavonoid intake and risk of chronic diseases. Am J Clin Nutr *76*: 560-568, 2002.

68 Adebamowo CA, Cho E, Sampson L, Katan MB, Spiegelman D, Willett WC and Holmes MD: Dietary flavonols and flavonolrich foods intake and the risk of breast cancer. Int J Cancer *114*: 628-633, 2005.

69 Arts IC, Jacobs DR Jr, Gross M, Harnack LJ and Folsom AR: Dietary catechins and cancer incidence among postmenopausal women: the Iowa Women's Health Study (United States). Cancer Causes Control *13*: 373-382, 2002

70 Hedelin M, Lof M, Olsson M, Adlercreutz H, Sandin S and Weiderpass E: Dietary phytoestrogens are not associated with risk of overall breast cancer but diets rich in coumestrol are inversely associated with risk of estrogen receptor and progesterone receptor negative breast tumors in Swedish women. J Nutr *138*: 938-945, 2008.

71 Wang L, Lee IM, Zhang SM, Blumberg JB, Buring JE and Sesso HD: Dietary intake of selected flavonols, flavones, and flavonoid-rich foods and risk of cancer in middle-aged and older women. Am J Clin Nutr *89*: 905-912, 2009.

72 Dong JY and Qin LQ: Soy isoflavones consumption and risk of breast cancer incidence or recurrence: a meta-analysis of prospective studies. Breast Cancer Res Treat *125*: 315-323, 2011.

73 Velentzis LS, Cantwell MM, Cardwell C, Keshtgar MR, Leathem AJ and Woodside JV: Lignans and breast cancer risk in pre- and post-menopausal women: meta-analyses of observational studies. Br J Cancer *100*: 1492-1498, 2009.

74 Buck K, Zaineddin AK, Vrieling A, Linseisen J and Chang-Claude J : Meta-analyses of lignans and enterolignans in relation to breast cancer risk. Am J Clin Nutr *92*: 141-153, 2010.

75 Touillaud MS, Thiebaut AC, Fournier A, Niravong M, Boutron-Ruault MC and Clavel-Chapelon F: Dietary lignan intake and postmenopausal breast cancer risk by estrogen and progesterone receptor status. J Natl Cancer Inst *99*: 475-486, 2007.

76 Sonestedt E, Borgquist S, Ericson U, Gullberg B, Olsson H, Adlercreutz H, Landberg G and Wirfält E: Enterolactone is differently associated with estrogen receptor beta-negative and -positive breast cancer in a Swedish nested case–control study. Cancer Epidemiol Biomarkers Prev *17*: 3241-3251, 2008.

77 Olsen A, Knudsen KE, Thomsen BL, Loft S, Stripp C, Overvad K, Møller S and Tjønneland A: Plasma enterolactone and breast cancer incidence by estrogen receptor status. Cancer Epidemiol Biomarkers Prev *13*: 2084-2089, 2004.

78 Ward HA, Kuhnle GG, Mulligan AA, Lentjes MA, Luben RN and Khaw KT: Breast, colorectal, and prostate cancer risk in the European Prospective Investigation into Cancer and Nutrition-Norfolk in relation to phytoestrogen intake derived from an improved database. Am J Clin Nutr *91*: 440-448, 2010.

79 Zamora-Ros R, Ferrari P, González CA, Tjønneland A, Olsen A, Bredsdorff L, Overvad K, Touillaud M, Perquier F, Fagherazzi G, Lukanova A, Tikk K, Aleksandrova K, Boeing H, Trichopoulou A, Trichopoulos D, Dilis V, Masala G, Sieri S, Mattiello A, Tumino R, Ricceri F, Bueno-de-Mesquita HB, Peeters PH, Weiderpass E, Skeie G, Engeset D, Menéndez V, Travier N, Molina-Montes E, Amiano P, Chirlaque MD, Barricarte A, Wallström P, Sonestedt E, Sund M, Landberg R, Khaw KT, Wareham NJ, Travis RC, Scalbert A, Ward HA, Riboli E and Romieu I: Dietary flavonoid and lignan intake and breast cancer risk according to menopause and hormone receptor status in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study. Breast Cancer Res Treat *139*: 163-117, 2013.

80 Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, Charrondière UR, Hémon B, Casagrande C, Vignat J, Overvad K, Tjønneland A, Clavel-Chapelon F, Thiébaut A, Wahrendorf J, Boeing H, Trichopoulos D, Trichopoulou A, Vineis P, Palli D, Bueno-De-Mesquita HB, Peeters PH, Lund E, Engeset D, González CA, Barricarte A, Berglund G, Hallmans G, Day NE, Key TJ, Kaaks R and Saracci R: European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr *5*: 1113-1124, 2002.

81 Adlercreutz H and Mazur W: Phyto-oestrogens and Western diseases. Ann Med *29*: 95-120, 1997.

82 Messina M, McCaskill-Stevens W and Lampe JW: Addressing the soy and breast cancer relationship: review, commentary, and workshop proceedings. J Natl Cancer Inst *98*: 1275-1284, 2006.

83 Webb AL and McCullough ML: Dietary lignans: potential role in cancer prevention. Nutr Cancer *51*: 117-131, 2005.

84 Kuiper GG, Carlsson B, Grandien K, Enmark E, Häggblad J, Nilsson S and Gustafsson JA : Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology *138*: 863-870, 1997.

85 Qin LQ, Xu JY, Wang PY and Hoshi K: Soyfood intake in the prevention of breast cancer risk in women: a meta-analysis of observational epidemiological studies. J Nutr Sci Vitaminol (Tokyo) *52*: 428-436, 2006.

86 Wu AH, Yu MC, Tseng CC and Pike MC: Epidemiology of soy exposures and breast cancer risk. Br J Cancer *98*: 9-14, 2008.

87 Mourouti N and Panagiotakos DB: Soy food consumption and breast cancer MR. Maturitas *76*: 118-122, 2013.

88 Trock BJ, Hilakivi-Clarke L and Clarke R:. Meta-analysis of soy intake and breast cancer risk. J Natl Cancer Inst *98*: 459-471, 2006.

89 de Lemos ML: Effects of soy phytoestrogens genistein and daidzein on breast cancer growth. Ann Pharmacother *35*: 1118-1121, 2001.

90 Magee PJ and Rowland IR: Phyto-oestrogens, their mechanism of action: current evidence for a role in breast and prostate cancer. Br J Nutr *91*: 513-531, 2004.

91 Wada K, Nakamura K, Tamai Y, Tsuji M, Kawachi T, Hori A, Takeyama N, Tanabashi S, Matsushita S, Tokimitsu N and Nagata C: Soy isoflavone intake and breast cancer risk in Japan: from the Takayama study. Int J Cancer *133*: 952-960, 2013.

92 Anderson LN, Cotterchio M, Boucher BA, and Kreiger N: Phytoestrogen intake from foods, during adolescence and adulthood, and risk of breast cancer by estrogen and progesterone receptor tumor subgroup among Ontario women. Int J Cancer *132*: 1683-1692, 2013.

93 Zaineddin AK, Buck K, Vrieling A, Heinz J, Flesch-Janys D, Linseisen J and Chang-Claude J: The association between dietary lignans, phytoestrogen-rich foods, and fiber intake and postmenopausal breast cancer risk: a German case-control study. Nutr Cancer *64*: 652-665, 2012.

94 Fritz H, Seely D, Flower G, Skidmore B, Fernandes R, Vadeboncoeur S, Kennedy D, Cooley K, Wong R, Sagar S, Sabri E and Fergusson D: Soy, red clover, and isoflavones and breast cancer: a systematic review. PLoS One *8*: e81968, 2013.

95 Higdon JV, Delage B, Williams DE and Dashwood RH: Cruciferous vegetables and human cancer risk: epidemiologic evidence and mechanistic basis. Pharmacol Res *55*: 224-236, 2007.

96 Johnson IT: Phytochemicals and cancer. Proc Nutr Soc *66*: 207-215, 2007.

97 Cade JE, Burley VJ and Greenwood DC; UK Women's Cohort Study Steering Group: Dietary fibre and risk of breast cancer in the UK Women's Cohort Study. Int J Epidemiol *36*: 431-438, 2007

98 Smith-Warner SA, Spiegelman D, Yaun SS, Adami HO, Beeson WL, van den Brandt PA, Folsom AR, Fraser GE, Freudenheim JL, Goldbohm RA, Graham S, Miller AB, Potter JD, Rohan TE, Speizer FE, Toniolo P, Willett WC, Wolk A, Zeleniuch-Jacquotte A and Hunter DJ: Intake of fruits and vegetables and risk of breast cancer: a pooled analysis of cohort studies. JAMA *285*: 769-776, 2001.

99 Terry P, Jain M, Miller AB, Howe GR and Rohan TE: No association among total dietary fiber, fiber fractions, and risk of breast cancer. Cancer Epidemiol Biomarkers Prev *11*: 1507-1508, 2002.

100 Suzuki R, Orsini N, Saji S, Key TJ and Wolk A: Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status – a meta-analysis. Int J Cancer *124*: 698-712, 2009.

101 Jung S, Spiegelman D, Baglietto L, Bernstein L, Boggs DA, van den Brandt PA, Buring JE, Cerhan JR, Gaudet MM, Giles GG, Goodman G, Hakansson N, Hankinson SE, Helzlsouer K, Horn-Ross PL, Inoue M, Krogh V, Lof M, McCullough ML, Miller AB, Neuhouser ML, Palmer JR, Park Y, Robien K, Rohan TE, Scarmo S, Schairer C, Schouten LJ, Shikany JM, Sieri S, Tsugane S, Visvanathan K, Weiderpass E, Willett WC, Wolk A, Zeleniuch-Jacquotte A, Zhang SM, Zhang X, Ziegler RG and Smith-Warner SA: Fruit and vegetables intake and risk of breast cancer by hormone receptor status. J Natl Cancer Inst *105*: 219-236, 2013.

102 Boggs DA, Palmer JR, Wise LA, Spiegelman D, Stampfer MJ, Adams-Campbell LL and Rosenberg L: Fruit and vegetable intake in relation to risk of breast cancer in the Black Women's Health Study. Am J Epidemiol *172*: 1268-1279, 2010.

103 Zhang X, Spiegelman D, Baglietto L, Bernstein L, Boggs DA, van den Brandt PA, Buring JE, Gapstur SM, Giles GG, Giovannucci E, Goodman G, Hankinson SE, Helzlsouer KJ, Horn-Ross PL, Inoue M, Jung S, Khudyakov P, Larsson SC, Lof M, McCullough ML, Miller AB, Neuhouser ML, Palmer JR, Park Y, Robien K, Rohan TE, Ross JA, Schouten LJ, Shikany JM, Tsugane S, Visvanathan K, Weiderpass E, Wolk A, Willett WC, Zhang SM, Ziegler RG and Smith-Warner SA: Carotenoid intakes and risk of breast cancer defined by estrogen receptor and progesterone receptor status: a pooled analysis of 18 prospective cohort studies. Am J Clin Nutr *95*: 713-725, 2012.

104 Eliassen AH, Hendrickson SJ, Brinton LA, Buring JE, Campos H, Dai Q, Dorgan JF, Franke AA, Gao YT, Goodman MT, Hallmans G, Helzlsouer KJ, Hoffman-Bolton J, Hultén K, Sesso HD, Sowell AL, Tamimi RM, Toniolo P, Wilkens LR, Winkvist A, Zeleniuch-Jacquotte A, Zheng W and Hankinson SE: Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies. J Natl Cancer Inst *104*: 1905-1916, 2012.

105 Fung TT, Chiuve SE, Willett WC, Hankinson SE, Hu FB and Holmes MD: Intake of specific fruits and vegetables in relation to risk of estrogen receptor-negative breast cancer among postmenopausal women. Breast Cancer Res Treat *138*: 925-930, 2013.

106 Johnson SA and Arjmandi BH: Evidence for anti-cancer properties of blueberries: a mini-review. Anticancer Agents Med Chem *13*: 1142-1148, 2013.

107 Masala G, Assedi M, Bendinelli B, Ermini I, Sieri S, Grioni S, Sacerdote C, Ricceri F, Panico S, Mattiello A, Tumino R, Giurdanella MC, Berrino F, Saieva C and Palli D: Fruit and vegetables consumption and breast cancer risk: the EPIC Italy study.Breast Cancer Res Treat *132*: 1127-1136, 2012.

108 Tamini RM, Hankinson SE, Campos H, Spiegelman D, Zhang S, Colditz GA, Willett WC and Hunter DJ: Plasma carotenoids, retinol, and tocopherols and risk of breast cancer. Am J Epidemiol *161*: 153-160, 2005.

109 Adams LS, Phung S, Yee N, Seeram NP, Li L and Chen S: Blueberry phytochemicals inhibit growth and metastatic potential of MDA-MB-231 breast cancer cells through modulation of the phosphatidylinositol 3-kinase pathway. Cancer Res *70*: 3594-3605, 2010.

110 Faria A, Pestana D, Teixeira D, de Freitas V, Mateus N and Calhau C: Blueberry anthocyanins and pyruvic acid adducts: anticancer properties in breast cancer cell lines. Phytother Res *24*: 1862-1869, 2010.

111 Somassagara RR, Hegde M, Chiruvella KK Musini A, Choudhary B and Raghavan SC: Extracts of strawberry fruits induce intrinsic pathway of apoptosis in breast cancer cells and inhibits tumour progression in mice. PLoS ONE *7*: e47021, 2012.

112 Noratto G, Porter W, Byrne D, Cisneros-Zevallos L: Identifying peach and plum polyphenols with chemopreventive potential against estrogen-independent breast cancer cells. J Agric Food Chem *57*: 5219-5226, 2009.

113 Karas M, Amir H, Fishman D, Danilenko M, Segal S, Nahum A, Koifmann A, Giat Y, Levy J, Sharoni Y: Lycopene interferes with cell cycle progression and insulin-like growth factor I signaling in mammary cancer cells. Nutr Cancer *36*: 101-111, 2000.

114 Gloria NF, Soares N, Brand C, Gloria NF, Soares N, Brand C, Oliveira FL, Borojevic R and Teodoro AJ: Lycopene and beta-carotene induce cell-cycle arrest and apoptosis in human breast cancer cell lines. Anticancer Res *34*: 1377-1386, 2014.

115 Takeshima M, Ono M, Higuchi T, Chen C, Hara T and Nakano S: Anti-proliferative and apoptosis-inducing activity of lycopene against three subtypes of human breast cancer cell lines. Cancer Sci *105*: 252-257, 2014.

116 Dorgan JF, Sowell A, Swanson CA, Potischman N, Miller R and Schussler N and Stephenson HE Jr: Relationships of serum carotenoids, retinol, alpha-tocopherol, and selenium with breast cancer risk: results from a prospective study in Columbia, Missouri (United States). Cancer Causes Control *9*: 89-97, 1998.

117 Kabat GC, Kim M, Adams-Campbell LL, Caan BJ, Chlebowski RT, Neuhouser ML, Shikany JM and Rohan TE; WHI Investigators: Longitudinal study of serum carotenoid, retinol, and tocopherol concentrations in relation to breast cancer risk among postmenopausal women. Am J Clin Nutr *90*: 162-169, 2009.

118 Hu F, Wang Yi B, Zhang W, Liang J, Lin C, Li D, Wang F, Pang D and Zhao Y: Carotenoids and breast cancer risk: a meta-analysis and meta-regression. Breast Cancer Res Treat *131*: 239-253, 2012.

119 Llanos AA, Peng J, Pennell ML, Krok JL, Vitolins MZ, Degraffinreid CR and Paskett ED : Effects of tomato and soy on serum adipokine concentrations in postmenopausal women at increased breast cancer risk: a cross-over dietary intervention trial. J Clin Endocrinol Metab *99*: 625-632, 2014.

120 Wang L, Li B, Pan MX, Mo XF, Chen YM and Zhang CX: Specific carotenoid intake is inversely associated with the risk of breast cancer among Chinese women. Br J Nutr *111*: 1686-1695, 2014.

121 Tamimi RM, Colditz GA and Hankinson SE: Circulating carotenoids, mammographic density, and subsequent risk of breast cancer. Cancer Res *69*: 9323-9329, 2009.

122 Voskuil DW, Vrieling A, Korse CM, Beijnen JH, Bonfrer JM, van Doorn J, Kaas R, Oldenburg HS, Russell NS, Rutgers EJ, Verhoef S, van Leeuwen FE, van't Veer LJ and Rookus MA: Effects of lycopene on the insulin-like growth factor (IGF) system in premenopausal breast cancer survivors and women at high familial breast cancer risk. Nutr Cancer *60*: 342-353, 2008.

123 Dusso AS, Brown AJ and Slatopolsky E: Vitamin D. Am J Physiol RenalPhysiol *289*: F8–-

124 Colston KW and Hansen CM: Mechanisms implicated in the growth regulatory effects of vitamin D in breast cancer. Endocrine-Related Cancer *9*: 45-59, 2002.

125 Cui Y and Rohan TE: Vitamin D, calcium, and breast cancer risk: a review.Cancer Epidemiol Biomarkers Prev *15*: 1427-1437, 2006.

126 Welsh J: Vitamin D and prevention of breast cancer. Acta Pharmacol Sin *28*: 1373-1382, 2007.

127 John EM, Schwartz GG, Dreon DM and Koo J: Vitamin D and breast cancer risk: the NHANES I Epidemiologic follow-up study, 1971-1975 to 1992. National Health and Nutrition Examination Survey. Cancer Epidemiol Biomarkers Prev *8*: 399-406, 1999.

128 Chen P, Hu P, Xie D, Qin Y, Wang F and Wang H : Meta-analysis of vitamin D, calcium and the prevention of breast cancer. Breast Cancer Res Treat *121*: 469-477, 2010.

129 Gissel T, Rejnmark L, Mosekilde L and Vestergaard P: Intake of vitamin D and risk of breast cancer – a meta-analysis. J Steroid Biochem Mol Biol *111*: 195-199, 2008.

130 Lappe J, Cullen D, Haynatzki G, Recker R, Ahlf R and Thompson K: Calcium and vitamin d supplementation decreases incidence of stress fractures in female navy recruits. J Bone Miner Res *23*: 741-749, 2008.

131 Anderson LN, Cotterchio M, Vieth R and Knight JA: Vitamin D and calcium intakes and breast cancer risk in pre- and postmenopausal women. Am J Clin Nutr 91: 1699-1707, 2010.

132 Chung M, Balk EM, Brendel M, Ip S, Lau J, Lee J, Lichtenstein A, Patel K, Raman G, Tatsioni A, Terasawa T and Trikalinos TA: Vitamin D and calcium: a systematic review of health outcomes. Evid Rep Technol Assess *183*: 1-420, 2009.

133 Abbas S, Linseisen J, Rohrmann S, Chang-Claude J, Peeters PH, Engel P, Brustad M, Lund E, Skeie G, Olsen A, Tjønneland A, Overvad K, Boutron-Ruault MC, Clavel-Chapelon F, Fagherazzi G, Kaaks R, Boeing H, Buijsse B, Adarakis G, Ouranos V, Trichopoulou A, Masala G, Krogh V, Mattiello A, Tumino R, Sacerdote C, Buckland G, Suárez MV, Sánchez MJ, Chirlaque MD, Barricarte A, Amiano P, Manjer J, Wirfält E, Lenner P, Sund M, Bueno-de-Mesquita HB, van Duijnhoven FJ, Khaw KT, Wareham N, Key TJ, Fedirko V, Romieu I, Gallo V, Norat T, Wark PA and Riboli E: Dietary intake of vitamin D and calcium and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition. Nutr Cancer *65*: 178-187, 2013.

134 Engel P, Fagherazzi G, Boutten A, Dupré T, Mesrine S, Boutron-Ruault MC and Clavel-Chapelon F: Serum 25(OH) vitamin D and risk of breast cancer: a nested case-control study from the French E3N cohort. Cancer Epidemiol Biomarkers Prev *19*: 2341-2350, 2010.

135 Yin L, Grandi N, Raum E, Haug U, Arndt V and Brenner H: Meta-analysis: serum vitamin D and breast cancer risk. Eur J Cancer *46*: 2196-2205, 2010.

136 Eliassen AH, Spiegelman D, Hollis BW, Horst RL, Willett WC and Hankinson SE: Plasma 25-hydroxyvitamin D and risk of breast cancer in the Nurses' Health Study II. Breast Cancer Res *13*: R50, 2011.

137 Mohr SB, Gorham ED, Alcaraz JE, Kane CJ, Macera CA, Parsons JK, Wingard DL and Garland CF: Serum 25-hydroxyvitamin D and prevention of breast cancer: pooled analysis. Anticancer Res *31*: 2939-2948, 2011.

138 Amir E, Cecchini RS, Ganz PA, Costantino JP, Beddows S, Hood N and Goodwin PJ: 25-Hydroxy vitamin-D, obesity, and associated variables as predictors of breast cancer risk and tamoxifen benefit in NSABP-P1. Breast Cancer Res Treat *133*: 1077-1088, 2012.

139 Kühn T, Kaaks R, Becker S, Eomois PP, Clavel-Chapelon F, Kvaskoff M, Dossus L, Tjønneland A, Olsen A, Overvad K, Chang-Claude J, Lukanova A, Buijsse B, Boeing H, Trichopoulou A, Lagiou P, Bamia C, Masala G, Krogh V, Sacerdote C, Tumino R, Mattiello A, Buckland G, Sánchez MJ, Menéndez V, Chirlaque MD, Barricarte A, Bueno-de-Mesquita HB, van Duijnhoven FJ, van Gils CH, Bakker MF, Weiderpass E, Skeie G, Brustad M, Andersson A, Sund M, Wareham N, Khaw KT, Travis RC, Schmidt JA, Rinaldi S, Romieu I, Gallo V, Murphy N, Riboli E and Linseisen J: Plasma 25-hydroxyvitamin D and the risk of breast cancer in the European prospective investigation into cancer and nutrition: A nested case-control study. Int J Cancer *133*: 1689-1700, 2013.

140 Bauer SR, Hankinson SE, Bertone-Johnson ER and Ding EL: Plasma vitamin D levels, menopause, and risk of breast cancer: dose-response meta-analysis of prospective studies. Medicine (Baltimore) *92*: 123-131, 2013.

141 Holick MF: Vitamin D deficiency. N Engl J Med *357*: 266Y281, 2007.

142 Lappe J, Travers-Gustafson D, Davies KM, Recker RR and Heaney RP: Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr *85*: 1586-1591, 2007.

143 Avenell A, ManLennan G, Jenkinson DJ, McPherson GC, McDonald AM, Pant PR, Grant AM, Campbell MK, Anderson FH, Cooper C, Francis RM, Gillespie WJ, Robinson CM, Torgerson DJ and Wallace WA; RECORD Trial Group: Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). J Clin Endocrinol Metab *97*: 614-622, 2012.

144 Sperati F, Vici P, Maugeri-Saccà M, Stranges S, Santesso N, Mariani L, Giordano A, Sergi D, Pizzuti L, Di Lauro L, Montella M, Crispo A, Mottolese M and Barba M: Vitamin D supplementation and breast cancer prevention: a systematic review and meta-analysis of randomized clinical trials. PLoS One *8*: e69269, 2013.

145 Li M, Chen P, Li J, Xie D and Wang H: Review: The Impacts of Circulating 25-Hydroxyvitamin D Levels on Cancer Patient Outcomes: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab *99*: 2327-2336, 2014.

146 Kim Y and Je Y: Vitamin D intake, blood 25(OH)D levels, and breast cancer risk or mortality: a meta-analysis. Br J Cancer *110*: 2772-2784, 2014.

147 Mathiasen IS, Sergeev IN, Bastholm L, Elling F, Norman AW and Jäättelä M: Calcium and calpain as key mediators of apoptosis-like death induced by vitamin D compounds in breast cancer cells. J Biol Chem 277: 30738–30745, 2002.

148 Chlebowski RT, Johnson KC, Kooperberg C, Pettinger M, Wactawski-Wende J, Rohan T, Rossouw J, Lane D, O'Sullivan MJ, Yasmeen S, Hiatt RA, Shikany JM, Vitolins M, Khandekar J and Hubbell FA; Women's Health Initiative Investigators: Calcium plus vitamin D supplementation and the risk of breast cancer. J Natl Cancer Inst 100: 1581-1591, 2008.

149 Crew KD, Shane E, Cremers S, McMahon DJ, Irani D and Hershman DL: High prevalence of vitamin D deficiency despite supplementation in premenopausal women with breast cancer undergoing adjuvant chemotherapy. J Clin Oncol *27*: 2151-2156, 2009.

150 Greenwald P, Anderson D, Nelson SA and Taylor PR: Clinical trials of vitamin and mineral supplements for cancer prevention. Am J Clin Nutr *85*: 314S-317S, 2007.

151 Nagel G, Linseisen J, van Gils CH, Peeters PH, Boutron-Ruault MC, Clavel-Chapelon F, Romieu I, Tjønneland A, Olsen A, Roswall N, Witt PM, Overvad K, Rohrmann S, Kaaks R, Drogan D, Boeing H, Trichopoulou A, Stratigakou V, Zylis D, Engeset D, Lund E, Skeie G, Berrino F, Grioni S, Mattiello A, Masala G, Tumino R, Zanetti R, Ros MM, Bueno-de-Mesquita HB, Ardanaz E, Sánchez MJ, Huerta JM, Amiano P, Rodríguez L, Manjer J, Wirfält E, Lenner P, Hallmans G, Spencer EA, Key TJ, Bingham S, Khaw KT, Rinaldi S, Slimani N, Boffetta P, Gallo V, Norat T and Riboli E: Dietary beta-carotene, vitamin C and E intake and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). Breast Cancer Res Treat *119*: 753-765, 2010.

152 Paski SC and Xu Z: Growth factor stimulated cell proliferation is accompanied by an elevated labile intracellular pool of zinc in 3T3 cells. Can J Physiol. Pharmacol *80*: 790-795, 2002.

153 Haase H and Rink L: Zinc signals and immune function. Biofactors *40*: 27-40, 2014.

154 Pan SY, Zhou J, Gibbons L, Morrison H and Wen SW; Canadian Cancer Registries Epidemiology Research Group [CCRERG]: Antioxidants and breast cancer risk- a population-based case-control study in Canada. BMC Cancer *11*: 372, 2011.

155 Pierpaoli E, Viola V, Barucca A, Orlando F, Galli F and Provinciali M: Effect of annatto-tocotrienols supplementation on the development of mammary tumors in HER-2/neu transgenic mice. Carcinogenesis *34*: 1352-1360, 2013.

156 Ahn KS, Sethi G, Krishnan K and Aggarwal BB: *et al*. c-Tocotrienol inhibits nuclear factor-jb signaling pathway through inhibition of receptor-interacting protein and TAK1 leading to suppression of antiapoptotic gene products and potentiation of apoptosis. J. Biol.Chem *282*: 809-820, 2007.

157 Loganathan R, Selvaduray KR, Nesaretnam K and Radhakrishnan AK: Tocotrienols promote apoptosis in human breast cancer cells by inducing poly(ADP-ribose) polymerase cleavage and inhibiting nuclear factor kappa-B activity. Cell Prolif *46*: 203-213, 2013.

158 Kim YI: Folate and DNA methylation: a mechanistic link between folate deficiency and colorectal cancer? Cancer Epidemiol Biomarkers Prev *13*: 511-519, 2004.

159 Larsson SC, Giovannucci E and Wolk A: Folate and risk of breast cancer: a meta-analysis. J Natl Cancer Inst *99*: 64-76, 2007.

160 Lewis SJ, Harbord RM, Harris R and Smith GD: Meta-analyses of observational and genetic association studies of folate intakes or levels and breast cancer risk. J Natl Cancer Inst *98*: 1607-1622, 2006.

161 Ma E, Iwasaki M, Kobayashi M, Kasuga Y, Yokoyama S, Onuma H, Nishimura H, Kusama R and Tsugane S: Dietary intake of folate, vitamin B2, vitamin B_6, vitamin B_{12}, genetic polymorphism of related enzymes, and risk of breast cancer: a case-control study in Japan. Nutr Cancer *61*: 447-456, 2009.

162 Maruti SS, Ulrich CM and White E: Folate and one-carbon metabolism nutrients from supplements and diet in relation to breast cancer risk. Am J Clin Nutr *89*: 624-633, 2009.

163 Shrubsole MJ, Shu XO, Li HL, Cai H, Yang G, Gao YT, Gao J and Zheng W: Dietary B vitamin and methionine intakes and breast cancer risk among Chinese women. Am J Epidemiol *173*: 1171-1182, 2011.

164 Bassett JK, Baglietto L, Hodge AM, Severi G, Hopper JL, English DR and Giles GG: Dietary intake of B vitamins and methionine and breast cancer risk. Cancer Causes Control *24*: 1555-1563, 2013.

165 Yang D, Baumgartner RN, Slattery ML, Wang C, Giuliano AR, Murtaugh MA, Risendal BC, Byers T and Baumgartner KB: Dietary intake of folate, B-vitamins and methionine and breast cancer risk among Hispanic and non-Hispanic white women. PLoS One *8*: e54495, 2013.

166 Weiwei Z, Liping C and Dequan L: Association between dietary intake of folate, vitamin B6, B12 & MTHFR, MTR Genotype and breast cancer risk Pak J Med Sci *30*: 106-110, 2014.

167 Ma E, Iwasaki M, Kobayashi M, Kasuga Y, Yokoyama S, Onuma H, Nishimura H, Kusama R and Tsugane S: Dietary intake of folate, vitamin B2, vitamin B6, vitamin B12, genetic polymorphism of related enzymes, and risk of breast cancer: a case-control study in Japan. Nutr Cancer *61*: 447-456, 2009.

168 Lin J, Lee IM, Cook NR, Selhub J, Manson JE, Buring JE and Zhang SM: Plasma folate, vitamin B-6, vitamin B-12, and risk of breast cancer in women. Am J Clin Nutr *87*: 734-743, 2008.

169 Singletary KW and Gapstur SM: Alcohol and breast cancer: review of epidemiologic and experimental evidence and potential mechanisms. JAMA *286*: 2143-2151, 2001.

170 Smith-Warner SA, Spiegelman D, Yaun SS, van den Brandt PA, Folsom AR, Goldbohm RA, Graham S, Holmberg L, Howe GR, Marshall JR, Miller AB, Potter JD, Speizer FE, Willett WC, Wolk A and Hunter DJ: Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA *279*: 535-540, 1998.

171 Knight JA, Bernstein L, Largent J, Capanu M, Begg CB, Mellemkjaer L, Lynch CF, Malone KE, Reiner AS, Liang X, Haile RW, Boice JD Jr; WECARE Study Collaborative Group and Bernstein JL: Alcohol intake and cigarette smoking and risk of a contralateral breast cancer: The Women's Environmental Cancer and Radiation Epidemiology Study. Am J Epidemiol *169*: 962-968, 2009.

172 Dumitrescu RG and PG Shields: The etiology of alcohol-induced breast cancer. Alcohol *35*: 213-225, 2005.

173 Halsted CH, Villanueva JA, Devlin AM and Chandler CJ: Metabolic interactions of alcohol and folate. J Nutr *132*: 2367S-2372S, 2002.

174 Gao CM, Ding JH, Li SP, Liu YT, Qian Y, Chang J, Tang JH and Tajima K: Active and passive smoking, and alcohol drinking and breast cancer risk in chinese women. Asian Pac J Cancer Prev *14*: 993-996, 2013.

175 Fagherazzi G, Vilier A, Boutron-Ruault MC, Mesrine S and Clavel-Chapelon F : Alcohol consumption and breast cancer risk subtypes in the E3N-EPIC cohort. Eur J Cancer Prev. 2014 Apr 16. [Epub ahead of print].

Received August 6, 2014
Revised September 11, 2014
Accepted September 18, 2014