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Review

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

ROBERTA ELISA ROSSI^{1,2}, MARINOS PERICLEOUS¹, DALVINDER MANDAIR^{1,3},
 TARA WHYAND⁴ and MARTYN EVAN CAPLIN¹

¹Centre for Gastroenterology and ⁴Department of Nutrition & Dietetics, Royal Free Hospital, London, U.K.;

²Gastroenterology and Endoscopy Unit, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico and Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy;

³Cancer Institute, University College London, Huntley Street, London, U.K.

Abstract. *Background: Breast cancer (BC) is the leading global cause of cancer death in women. There is growing evidence for a role for dietary factors in BC pathophysiology. Aim: To evaluate the impact of dietary factors in BC risk. Methods: Bibliographical searches were performed in PubMed, using the following keywords: “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 minimised 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 is 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 needed but are difficult to design due to the number of variable factors.

Breast cancer (BC) is currently the most frequently diagnosed cancer and the leading global cause of cancer 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).

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

Methods

Bibliographical searches were performed in PubMed using the following keywords, including both medical subject heading

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.

(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 “Fruit 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-response 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 as increased adiposity (18). In a recent prospective cohort study, including 88,803 premenopausal 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 intakes 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 development.

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)+/progesterone 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 identified 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 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 tumorigenesis 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 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 particularly 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 has been 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 metabolised 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 oestrogen 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 analysed 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 subgroups 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 suggesting 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.

Fruit 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 fibre (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 association (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-tumour 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 tumour progression by enhancing apoptosis (111). Additionally, peaches' extract may reduce proliferation in oestrogen-independent BC cell lines (112).

Conclusion: There is evidence supporting 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 premenopausal 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 suggesting 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 & Beta-carotene, Folate & 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 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 in 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 dysregulation 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 μ g/day) and vitamin B6 (<0.84 mg/day) and increased BC risk, suggesting that folate and other methyl-related B vitamins

Table I. Summary of current evidence about 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 findings.

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.

have a role in developing BC (166). These findings are consistent 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 minimised. 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 conflict of interest.

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