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Review

Chemoprevention of Breast Cancer With Vitamins and Micronutrients: A Concise Review

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Abstract. *Numerous dietary components and vitamins have been found to inhibit the molecular events and signalling pathways associated with various stages of breast cancer development. To identify the vitamins and dietary micronutrients that exert protective effects against breast cancer and define their mechanism of action, we performed a literature review of in vitro, animal and epidemiological studies and selected the in vitro and animal studies with robust molecular evidence and the epidemiological studies reporting statistically significant inverse associations for a breast cancer-specific protective effect. There is sufficient evidence from in vitro, animal and epidemiological human studies that certain vitamins, such as vitamin D3, folate, vitamin B6, and beta carotene as well as dietary micronutrients, such as curcumin, piperine, sulforaphane, indole-3-carbinol, quercetin, epigallocatechin gallate (EGCG) and omega-3 polyunsaturated fatty acids (PUFAs), display an antitumoral activity against breast cancer and have the potential to offer a natural strategy for breast cancer chemoprevention and reduce the risk of breast cancer recurrence. Therefore, a supplement that contains these micronutrients, using the safest form and dosage should be investigated in future breast cancer chemoprevention studies and as part of standard breast cancer therapy.*

Breast cancer remains a very common disease among women, with an annual global incidence of over 2 million cases per year and one of the highest numbers of cancer-related deaths among women (1, 2). The limitations of current treatment strategies include: i) resistance to drug treatment, ii) significant side-effects and iii) cost. The high incidence and limitations of therapeutic strategies underscore the importance of pursuing prevention strategies that lack significant adverse effects. Numerous dietary components and vitamins have been found to inhibit the molecular events and signalling pathways associated with various stages of breast cancer development and could, therefore, represent potential strategies in breast cancer chemoprevention. A major factor in the effectiveness of these components lies in their natural, raw form. It should be highlighted that cooking can cause considerable losses in essential vitamins and micronutrients (3-7).

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Key Words: Vitamins, micronutrient, phytochemicals, diet, cruciferous vegetables, breast cancer, chemoprevention, review.

Materials and Methods

We conducted a literature review of epidemiological studies reporting breast cancer-specific risks in relation to serum levels of vitamins and micronutrients. *In vitro* and animal studies investigating the effects of such micronutrients and vitamins on breast tumours and breast cancer cells were also included in our search. Searches were conducted using the PubMed search engine from inception until May 2019 and the following search terms were used: 'micronutrients, vitamins, diet and breast cancer'. A total of 3793 abstracts that fitted our initial search criteria were further assessed for relevance and consistency and a total of 104 studies were finally selected. Studies demonstrating statistically significant inverse associations (epidemiological studies) or robust molecular evidence (animal and *in vitro* studies) for a protective effect were selected to identify the vitamins and micronutrients to be covered in our concise review. When conflicting results were found the most updated meta analyses were included in this review. Vitamins and micronutrients associated with no evidence, weak or frequently inconsistent evidence for protective effects against breast cancer were not included in this review. The relative risk (RR) or hazard ratio (HR) and 95% confidence intervals (CI) were reported for the relevant studies.

Results

We identified 4 vitamins: i) vitamin D3, ii) folate, iii) vitamin B6, and iv) beta carotene, 2 spices: i) curcumin and ii) piperine and 5 micronutrients: i) sulforaphane, ii) indole-3-carbinol, iii) quercetin, iv) epigallocatechin gallate (EGCG)

and v) omega-3 polyunsaturated fatty acids (PUFAs) associated with lower risks of breast cancer risk and/or recurrence. The epidemiological studies demonstrating the protective effects of these vitamins and micronutrients against breast cancer were assessed and presented in Table I. Results of this literature search for the mechanisms of action by which these vitamins and micronutrients exert their chemo-preventive effects on breast cancer are shown in Table II.

Folate (vitamin B9). Vitamin B9 is an essential nutrient that naturally occurs as folate. A pooled analysis of 23 prospective studies involving a total of 41,516 breast cancer cases and 1,171,048 individuals were included for meta-analysis. Folate intake was found to be associated with an 18% decrease in risk of developing hormone receptor negative breast cancer [relative risk (RR)=0.82, 95% confidence interval (CI)=0.68-0.97]. An increment of folate intake of 100 micrograms per day was associated with a 10% decrease in risk among women who drink moderate amounts of alcohol (RR=0.90, 95%CI=0.85-0.97) (8).

Furthermore, BRCA1 mutation carriers who used any folic acid-containing supplement had a significantly decreased risk of breast cancer (55%) compared to women who never used a folic acid-containing supplement [odds ratio (OR)=0.45, 95%CI=0.25-0.79, p=0.006] (9). Finally, relatively high dietary intake of folate intake was inversely associated with risk of cancer of the womb and the ovaries. Women with folate in the highest quartile had a lower risk of endometrial cancer than those with folate levels in the lowest quartile with 48% risk reduction (HR=0.52; 95%CI=0.29-0.93). Women in the upper third for folate intake had lower risk of ovarian cancer than those in the lowest third with 61% risk reduction (HR=0.39, 95%CI=0.19-0.80) (10). Therefore, it makes sense for women to take a daily folate supplement (400 micrograms daily). This is a healthier form of vitamin B9 compared to folic acid.

Vitamin D3. It has been demonstrated that treating breast cancer cells with 1,25-dihydroxy (OH) vitamin D3 induces two beneficial effects: i) an anti-proliferative effect suppressing growth of cells and ii) a pro-apoptotic effect encouraging natural breast cancer cell death (11, 12).

A recent meta-analysis of 68 studies published in 2018 showed a protective effect of 1.25(OH)D3 use and breast cancer, with a 35% reduction in risk observed in case-control studies (OR=0.65, 95%CI=0.56-0.76) and 15% risk reduction in cohort studies (RR=0.85, 95%CI=0.74-0.98). Interestingly, the protective vitamin D – breast cancer association persisted only in premenopausal women, with a 33% risk reduction (OR=0.67, 95%CI=0.49-0.92), when restricting the analysis to nested case-control studies (13).

A more recent meta-analysis has demonstrated that vitamin D deficiency was directly related to breast cancer risk (RR_{pooled}=1.91, 95%CI=1.51-2.41, p<0.001) while total blood vitamin D levels (RR_{pooled}=0.99, 95%CI=0.97-1.00, p=0.022, per 100 IU/d) and supplemental vitamin D intakes (RR_{pooled}=0.97, 95%CI=0.95-1.00, p=0.026) had a protective effect (14).

Finally, a meta-analysis of five studies including 4,413 breast cancer patients showed that higher 1.25(OH)D_3 levels (>75nmol/l) were associated with a 42% reduction in the odds of dying from breast cancer (HR_{pooled}=0.58, 95%CI=0.38-0.84) (15).

Vitamin B6. Vitamin B6 is involved in many biochemical reactions and may play a role in carcinogenesis. A combined analysis of data derived from 5 studies carried out in the United States, including 2,509 breast cancer cases, has showed that high serum pyridoxal 5'-phosphate levels (PLP is the active form of vitamin B6) were associated with a 20% reduction in breast cancer risk compared to low levels among postmenopausal women [combined RR for the highest *versus* lowest serum PLP levels was 0.80, 95%CI=0.66-0.98, p=0.03] (16).

A more comprehensive analysis in 2017 of 121 observational studies (participants=1,924,506, cancer cases=96,436) and 9 randomized controlled trials (RCTs) (participants=34,911, cases=2539) considering 19 tumour sites revealed that high intake of dietary (food only) vitamin B6 was significantly associated with 22% lower risk of all cancers (RR=0.78, 95%CI=0.73-0.84) (17).

Beta Carotene. Beta carotene is a precursor for vitamin A and is found predominantly in carrots, mango, maize, lentils, dark green leaves, amaranth, and spinach. A pooled analysis of eight cohort studies comprising more than 80% of the world's published prospective data on plasma or serum carotenoids and breast cancer, including 3,055 case subjects and 3,956 matched control subjects, revealed that high serum levels of beta carotene are associated with a 17% reduction in breast cancer risk (top *versus* bottom quintile RR=0.83, 95%CI=0.70-0.98, p-trend=0.02) (18). Furthermore, a meta-analysis of 10 studies (8 cohort, 1 clinical trial, and 1 pooled study) with 19,450 breast cancer cases, has shown that the dietary intake of β-carotene is significantly associated with improved breast cancer survival with a 30% reduction in the odds of dying from breast cancer [summary HR=0.70 (95%CI=0.50-0.99, I^2=37.5%) for the highest *versus* lowest intake of β-carotene] (19). In a large prospective analysis with 20 years of follow-up, women with high plasma carotenoids were at reduced breast cancer risk, particularly for more aggressive and ultimately fatal disease. Higher concentrations of β-carotene were associated with 28% significantly lower risk of breast cancer (β-carotene top *versus* bottom quintile RR=0.72, 95%CI=0.59-0.88, p-trend<0.001) (20).

Table I. *Summary of studies selected in our review reporting on risk estimates of the associations between intake of selected vitamins and micronutrients (highest vs. lowest) and breast cancer risk.*

Vitamin/ Micro-nutrient	Ref. no.	Study design	Population (case, participants)	Exposure	Risk estimate (95%CI)		Hetero-geneity test I^2 (%)	Outcome
					RR, HR, OR (95%CI)	*p*-Value for Trend		
Folate (Vitamin B9)	8	Meta-analysis of 23 prospective studies	41,516 breast cancer cases, 1,171,048 individuals	Dietary, supplemental, total intake and plasma levels	(RR=0.82 (95%CI:=0.68-0.97)			(ER)$^-$ negative /(PR)$^-$ negative breast cancer risk
					(RR=0.90, 95% CI=0.85-0.97)			(ER)– negative/(PR) –negative breast cancer risk: an increment of folate intake of 100 μg/day
					(RR=0.88, 95% CI=0.78-1.00)			(ER)– negative breast cancer risk
					(RR=0.94, 95% CI=0.88-0.99)			(ER)– negative breast cancer risk: an increment of folate intake of 100 μg/day
					(RR=0.82, 95% CI=0.72-0.94)			Breast cancer risk among women with moderate/high levels of alcohol consumption
	9	Case–control study	129 breast cancer cases, 271 controls	Supplemental use	(OR=0.45, 95%CI=0.250.79)	*p*=0.006		Breast cancer risk in *BRCA1* and *BRCA2* mutation carriers
					(OR=0.39)	*p*=0.01		Breast cancer risk and moderate supplement intake
					(OR=0.54)	*p*=0.09		Breast cancer risk and high supplement intake
	10	Pooled analysis of several studies (a case-cohort design)	3,185 women [breast (n=922), endometrial (n=180), ovarian (n=104)]	Dietary intake	(HR=0.52, 95%CI=0.29-0.93)	*p*=0.04		Endometrial cancer risk
					(HR=0.39, 95%CI=0.19-0.80)	*p*=0.01		Ovarian cancer risk
25(OH) vitamin	13	Meta-analysis of 68 studies		Dietary, supplemental, total and blood 25(OH) vitamin D	(OR_{pooled}=0.65, 95%CI=0.56-0.76)		I^2=40.87%	Breast cancer risk in case-control studies
					(RR_{pooled}=0.85, 95%CI=0.74-0.98)		I^2=3.56%	Breast cancer risk in cohort studies
					(OR_{pooled}=0.67, 95%CI=0.49-0.92)			Breast cancer risk among premenopausal women in nested case-control studies
	14	Meta-analysis of 22 case-control, cross-sectional, and prospective cohort studies	229,597 subjects	Dietary and blood 25(OH) vitamin D	(RR_{pooled}=1.91, 95%CI=1.51-2.41)	*p*<0.001		Breast cancer risk and serum 25(OH)D deficiency
					(RR_{pooled}=0.99, 95%CI=0.97-1.00)	*p*=0.022		Breast cancer risk and total blood vitamin D levels (per 100 IU/d)
					(RR_{pooled}=0.97, 95%CI=0.95-1.00)	*p*=0.026		Breast cancer risk and supplemental vitamin D intakes
	15	Meta-analysis of five studies	4,413 breast cancer cases	Serum 25(OH)D levels	(HR_{pooled}= 0.57 (0.38-0.84)		I^2=17%	Breast disease-specific mortality
					(HR_{pooled}=0.62 (0.49-0.78)		I^2=4.6%	Overall mortality among breast cancer patients
Vitamin B6	10	Pooled analysis of several studies (a case-cohort design)	3,185 women [breast (n=922), endometrial (n=180), ovarian (n=104)]	Dietary intake	(HR=0.59; 95% CI=0.38-0.93)	*p*=0.03		Breast cancer risk among premenopausal women
					(HR=0.49; 95% CI=0.24-0.98)	*p*=0.04		Ovarian cancer risk
	16	Pooled analysis of 5 studies	2,509 breast cancer cases	Serum PLP (pyridoxal 5'-phosphate) levels	(RR_{pooled}=0.80, 95%CI=0.66-0.98)	*p*=0.03	I^2=0.30%	Breast cancer risk
					(RR_{pooled}=0.71, 95%CI=0.57-0.88)	*p*<0.00	I^2=0.00%	Breast cancer risk among post-menopausal women
					(RR_{pooled}=0.77, 95%CI=0.69-0.86)	*p*<0.00		Breast cancer risk per 100 pmol ml^{-1} increment in PLP levels

Table I. *Continued*

Table I. *Continued*

Vitamin/ Micro-nutrient	Ref. no.	Study design	Population (case, participants)	Exposure	Risk estimate (95%CI)		Hetero-geneity test I^2 (%)	Outcome
					RR, HR, OR (95%CI)	*p*-Value for Trend		
		Pooled analysis of 4 studies	Two prospective cohort studies: 3898 breast cancer cases and 70,656 postmenopausal women, 718 breast cancer cases and 72,861 participants. One nested case-control study: 318 breast cancer cases and 647 controls. One case-control study: 391 breast cancer cases and 782 controls.	Combined intake of vitamin B_6 and folate	(RR_{pooled}=0.91, 95%CI=0.79-1.04)	*p*=0.17	I^2=0.00%	Breast cancer risk
	17	Meta-analysis 121 observational studies and 9 randomized controlled trials	121 observational studies (96,436 cancer cases in 19 tumour sites, 33 934 breast cancer, 1,924,506 subjects) 9 randomised controlled trials (2539 cases, 34,911 participants)	Dietary intake	(RR=0.88, 95%CI=0.78-0.98)	0.03	I^2=60.0	Breast cancer risk
					(RR=0.78, 95%CI=0.73-0.84)	4.21×10^{-12}	I^2=77.1	Risk of all cancers combined
				PLP blood levels	(RR=0.83, 95%CI=0.63-1.10)	0.20	I^2=40.9	Breast cancer risk
					(RR=0.66, 95% CI=0.58-0.76)	3.62×10^{-09}	I^2=50.8	Risk of all cancers combined
beta carotene	18	Pooled analysis of 8 prospective cohort studies	3,055 cases, 3,956 controls	Plasma or serum levels	(RR=0.83, 95%CI=0.70-0.98)	*p*=0.02		Breast cancer risk
					(RR=0.52, 95%CI=0.36-0.77)	*p*=0.001		$(ER)^-$ negative breast cancer risk
	19	Meta-analysis of 10 studies (8 cohort, 1 clinical trial, and 1 pooled study)	19,450 breast cancer cases	Dietary intake	(HR=0.70, 95%CI=0.50-0.99)		I^2=37.5%	Breast cancer overall survival
					(HR=0.93, 95%CI=0.88-0.99)		I^2=38.7%	Breast cancer overall survival per 1200 μg/day increment
	20	Nested case-control study	2188 cases, 2188 controls	Plasma concentrations	(RR=0.72, 95%CI=0.59-0.88)	*p*<0.001		Breast cancer risk
					(RR=0.32, 95%CI=0.21, 0.51)	*p*<0.001		Breast cancer recurrence and death
					(RR=0.62, 95%CI=0.47-0.83)	*p*<0.001		Breast cancer risk among women with BMI <25
					(RR=0.47, 95%CI=0.28-0.77)	*p*=0.003		Luminal B breast cancer risk
					(RR=0.32, 95%CI=0.21-0.51)	*p*<0.001		Risk of breast cancers that recurred or were ultimately lethal
					(RR=0.47, 95%CI:0.31-0.71)	*p*=0.002		Risk of recurrence and breast cancer death
Sulfo-	49	Meta-analysis	18,673 cases,	Cruciferous	(RR=0.85,		I^2=51.2%	Breast cancer risk

Table I. *Continued*

Table I. *Continued*

Vitamin/ Micro-nutrient	Ref. no.	Study design	Population (case, participants)	Exposure	Risk estimate (95%CI)		Hetero-geneity test I^2 (%)	Outcome
					RR, HR, OR (95%CI)	*p*-Value for Trend		
raphane & indole-3-carbinol		of 13 studies (11 case-control and 2 cohort studies)	165,236 subjects	vegetable intake	95%CI:=0.77-0.94)			
	50	Case-control study	1,485 cases, 1,506 controls	Cruciferous vegetable intake	(OR=0.51, 95%CI:=0.41-0.63)	$p<0.001$		Breast cancer risk
				Glucosinolates (GSL)	(OR=0.54, 95%CI=0.44-0.67)	$p<0.001$		Breast cancer risk
				Isothiocyanates (ITC)	(OR=0.62, 95%CI=0.50-0.76)			Breast cancer risk
	51	Case-control study	1,491 breast cancer cases, 1,482 controls	Cruciferous vegetable intake	(OR=0.68, 95%CI=0.55-0.86)	$p=0.0006$		Breast cancer risk
	52	Pooled analysis of a network of case-control studies	3,034 breast cancer cases, 11,492 controls	Cruciferous vegetable intake	(OR=0.83, 95%CI=0.74-0.94)			Breast cancer risk
					(OR=0.73, 95%CI=0.60-0.88)			Breast cancer risk among women ≥60 years
					(OR=0.76, 95%CI=0.64-0.91)			Breast cancer risk among women with high levels of alcohol consumption
					(OR=0.78, 95%CI=0.61-1.01)			Breast cancer risk among current smokers
	53	Large population-based case-control study	1,463 breast cancer cases, 1,500 controls	Leafy vegetables intake	(OR=0.66, 95%CI=0.50-0.86)	$p=0.03$		Breast cancer risk among postmenopausal women with (ER)+ positive tumours
				Vegetable intake	(OR=0.63, 95%CI=0.48-0.86)	$p<0.01$		Breast cancer risk
				Vegetables and fruits intake	(OR=0.65, 95%CI=0.51-0.82)			Breast cancer risk among women with (ER)+ positive tumours
				Vegetables and fruits intake	(OR=0.64, 95%CI=0.48-0.83)			Breast cancer risk among women with (ER)+ positive (PR)+ positive tumours
	54	Case-control study	740 breast cancer cases, 810 controls	Broccoli intake	(OR=0.6, 95%CI=0.40-1.01)	$p=0.058$		Breast cancer risk among premenopausal women
	63	Meta-analysis of 12 studies (6 prospective cohort studies, 6 case-control studies)	9,513 cases and 181,906 controls	Flavonols intake	(RR=0.88, 95%CI=0.80-0.98)			Breast cancer risk
	64	Pooled analysis of a network of multicentric case-control studies	10,000 cancer cases, 16,000 controls	Flavonols intake	OR=0.80 OR=0.63			Breast cancer risk Ovarian cancer risk
	65	Large case-control study	2,569 cancer cases, 2,588 controls	Flavonols intake	OR=0.80	$p=0.06$		Breast cancer risk

Table I. *Continued*

Table I. *Continued*

Vitamin/ Micro-nutrient	Ref. no.	Study design	Population (case, participants)	Exposure	Risk estimate (95%CI)		Hetero-geneity test I^2 (%)	Outcome
					RR, HR, OR (95%CI)	*p*-Value for Trend		
	66	Large case-control study	820 breast cancer cases, 1,548 controls	Flavonols intake	(OR=0.81, 95%CI=0.73-0.90)	*p*=0.001		Breast cancer risk, per 8.3 mg day−1increment of flavonols
	67	Large cohort study	9,865 at risk individuals 1,093 cancer cases in different sites, 125 breast cancer cases	Quercetin intake	(RR=0.77, 95%CI=0.65-0.92)	*p*=0.01		Risk of all cancers combined
					(RR=0.62, 95%CI=0.37-1.03)	*p*=0.25		Breast cancer risk
					(RR=0.54, *p*=0.14 95%CI=0.30-0.95)			Breast cancer risk when other dietary sources adjusted
Epigallo-catechin-3-gallate (EGCG)	82	Meta-analysis	5,617 breast cancer cases	Green tea consumption	(RR_{pooled}=0.73, 95%CI=0.56-0.96)			Risk of breast cancer recurrence
					(RR_{pooled}=0.81, 95%CI=0.75-0.88)			Breast cancer risk in case-control studies
	83	Meta-analysis of 8 cohort studies and 5 case- control studies	163,810 individuals	Green tea consumption	(RR=0.85, 95%CI=0.80-0.92)	*p*=0.000		Breast cancer risk
					(RR=0.81, 95%CI=0.74-0.88)	*p*=0.000		Risk of breast cancer recurrence
					(RR=0.88, 95%CI=0.78-0.99)	*p*=0.035		Breast cancer risk among pre-menopausal women
					(RR=0.81, 95%CI=0.74-0.88)	*p*=0.000		breast cancer risk in case-control studies
Omega-3 poly-unsaturated fatty acids (PUFAs)	93	Meta-analysis of 21 prospective cohort studies	20,905 breast cancer cases 883,585 participants	Total n-3 PUFA	(RR=0.86, 95%CI=0.78-0.94)		I^2=54%	Breast cancer risk
				Dietary marine n-3 PUFA intake	(RR=0.85, 95%CI=0.76-0.96)		I^2=67%	Breast cancer risk
				n-3 PUFA tissue biomarkers	(RR=0.86, 95% CI=0.71-1.03)		I^2=8%	Breast cancer risk
				Dietary marine n-3 PUFA intake	(RR=0.95, 95%CI=0.90-1.00)		I^2=52%	Breast cancer risk per 0.1 g/day increment of dietary n-3 PUFA intake
				Total n-3 PUFA	(RR=0.77, 95%CI=0.60-0.99)			Breast cancer risk in studies without adjustment for BMI
				Dietary marine n-3 PUFA intake	(RR=0.74, 95%CI=0.64-0.86)			Breast cancer risk in studies without adjustment for BMI
	94	Meta-analysis of 5 cohort studies and 6 prospective nested case-control studies	8,331 breast cancer cases 274,135 participants	Intake ratio of n-3/n-6 PUFA	(RR_{pooled}=0.90, 95%CI=0.82-0.99)		I^2=11.40%	Breast cancer risk
				Intake ratio of n-3/n-6 PUFA	(RR_{pooled}=0.94, 95%CI=0.90-0.99)	*p*=0.012	I^2=3.20%	Breast cancer risk per 1/10 increment of n-3/n-6 (PUFAs) ratio
				ratio of n-3/n-6 in serum phospholipids	(RR_{pooled}=0.62, 95%CI=0.39-0.97)	*p*=0.103	I^2=0.00%	Breast cancer risk in USA subjects with high n-3/n-6 PUFAs in serum phospholipids
				ratio of n-3/n-6 in serum phospholipids	(RR_{pooled}=0.73, 95%CI=0.59-0.91)	*p*=0.004	I^2=0.00%	Breast cancer risk per 1/10 increment of serum phospholipids of n-3/n-6 PUFAs ratio in USA subjects

CI: Confidence Interval; RR: relative risk; HR: hazard ratio: OR: odds ratio; ER: oestrogen receptor; PR: progesterone receptor.

Table II. *Summary of the mechanisms of action of the micronutrients and spices against breast cancer.*

Micronutrients and spices	Study Author(s), year (Ref.)	Main mechanism of action and key signalling pathways involved
Curcumin	Chang *et al*., 2012	Induction of cell cycle arrest
	Carvalho Ferreira *et al*., 2015	Induction of apoptosis
	Ravindran *et al*., 2009	Disruption of signalling within the tumour microenvironment
		Modulation of cancer immunity and cancer related micro RNAs
	Mukherjee *et al*., 2014 (21-24)	Inhibition of clonal expansion of breast cancer stem cells
		Inhibition of proliferation
		Inhibition of angiogenesis
		Key signalling pathways: NFkB, PI3K/Akt/mTOR MAPK and JAK/STAT
Piperine	Zheng *et al*., 2016	Induction of apoptosis
	Do *et al*., 2013	Inhibition of breast cancer cells migration
	Lai *et al*., 2012	Inhibition of proliferation
	Abdelhamed *et al*., 2014 (30-32, 36)	Key signalling pathways: (EGF)-mediated expression of both MMP-9 and MMP-13
Sulforaphane	Atwell *et al*., 2015	Induction of cell cycle arrest
	Jackson *et al*., 2004	Induction of apoptosis
	Pledgie-Tracy *et al*., 2007	Induction of oligonucleosomal DNA fragmentation
	Azarenko *et al*., 2008	Disruption of signalling within the tumour microenvironment
	Ramirez *et al*., 2009	Inhibition of proliferation
	Meeran *et al*., 2010 (39-44)	
Indole-3-carbinol	Katz *et al*., 2018	Induction of apoptosis
	Bosetti *et al*., 2002	Modulation of oestrogen metabolism
	Rahman *et al*., 2003	
	Aggarwal *et al*., 2005 (45-48)	
Quercetin	Chahar *et al*., 2011	Induction of TRAIL-mediated apoptosis
	Gibellini *et al*., 2011	Restoration of tumour suppressor
	Rauf *et al*., 2018	Modulation of epigenetic alterations
	Carlos-Reyes *et al*., 2019 (55-58)	Down-regulation of oncogene expression
		Up-regulation of tumour-suppressor genes expression
Epigallocatechin gallate (EGCG)	Yiannakopoulou, 2014	Induction of apoptosis
	Sur *et al*., 2017	Inhibition of matrix metalloproteinases (MMPs)
	Rafieian-Kopaei *et al*., 2017	Inhibition of vascular endothelial growth factor (VEGF)
	Beltz *et al*., 2006	Induction of reactive oxygen species (ROS)
	Xu *et al*., 1992	Inhibition of the formation of DNA adducts
	Narisawa *et al*., 1993	Inhibition of clonal expansion of breast cancer stem cells
	Kaur *et al*., 2007	Modulation of epigenetic alterations
	Lin *et al*., 2003	Downregulation of oncogene expression
	Gianfredi *et al*., 2017	Upregulation of tumour-suppressor genes expression
	Chikara *et al*., 2018	Inhibition of angiogenesis
	Thangapazham *et al*., 2007	Key signalling pathways: HER-2/neu, insulin-like growth factor-1,
	Min *et al*., 2012 (70-81)	(IGF-1)-mediated signalling, nuclear factor-κB (NF-κB), activator protein 1 (AP-1), MAPKs, cyclo-oxygenase-2 (COX2), nitric oxide synthesis, EGF-mediated signal transduction.
Omega-3 polyunsaturated fatty acids (PUFAs)	Karmali *et al*., 1984	Reduction in proinflammatory lipid derivatives
	Rose *et al*., 1991	Key signalling pathways: Growth factor receptor (EGFR),
	Chajès *et al*., 1995	the NF-κB mediated cytokine production, the mammalian target of
	Serini *et al*., 2017	rapamycin (mTOR), cyclooxygenase (COX) and
	Fabian *et al*., 2015 (88-92)	lipoxygenase (LOX) metabolic pathway.

Curcumin and piperine. Turmeric is a yellow spice with a specific flavour used in Asian cuisine. Curcumin, a polyphenolic compound, is a secondary metabolite isolated from turmeric. The anti-breast-cancer effects of Curcumin came mainly from investigators of animal and laboratory studies.

Curcumin influences breast development and progression through its effect on cell cycle and proliferation, natural cell death, cancer spread and development of new blood supply to support tumour progression (21, 22). The key signalling pathways involved include the NFkB, PI3K/Akt/mTOR, MAPK and JAK/STAT (23). Curcumin also mediates the

modulation of the tumour microenvironment, cancer immunity, breast cancer stem cells and cancer-related micro RNAs (24). The chemopreventive effect of curcumin towards mammary tumorigenesis has been observed in both the initiation and post-initiation phases and has been found to significantly inhibit the initiation of mammary adenocarcinoma (25, 26).

Despite the lack of evidence from human clinical studies, using curcumin as a therapeutic and preventive agent in breast cancer is supported by the extensive evidence derived from laboratory and animal studies, demonstrating a diverse biological activity against breast cancer cells and tumours, much of which remains inexplicable (27). Concomitant administration of piperine significantly enhances the extent of absorption, serum concentration and bioavailability of curcumin in humans up to 20-fold (28, 29).

Piperine has also been proved to exert anti breast cancer properties, mainly by inhibiting proliferation and promoting apoptosis (30). Experimental data have demonstrated that piperine can inhibit hormone-dependent breast cancer cells and strongly suppress epidermal growth factor (EGF)-mediated expression of both MMP-9 and MMP-13 in breast cancer cells, which is activated in up to one-third of breast cancer patients, leading to an inhibition of the migration of breast cancer cells (31, 32). In studying the anticancer effect of bioactive phytochemicals combined with conventional cancer therapies, piperine was found to potentiate the cytotoxicity of anti-cancer drugs and even reverse multi-drug resistance that impairs the efficacy of chemotherapy (33).

Furthermore, piperine has been found to enhance the sensitisation of HER2-overexpressing breast cancer cells to paclitaxel (Taxol®), a chemotherapy medication used to treat breast cancer (31, 34). A synergistic effect has also been observed with Tamoxifen against breast cancer cells (35). In triple-negative breast cancer, which is the most aggressive type of breast cancer and is poorly responsive to endocrine therapeutics, piperine has been found to trigger apoptosis *via* the mitochondrial pathway and augment the effectiveness of TRAIL-based therapeutics (36). In studying the combination of piperine with radiotherapy, the first was found to enhance the γ radiation cytotoxicity for triple-negative breast cancer and the combination of piperine and curcumin can sensitise breast cancer cells to radiation in a dose dependent manner (37, 38).

Sulforaphane and indole-3-carbinol. Numerous studies investigating the association of cruciferous vegetables intake with risk of breast cancer have reported that consumption of cruciferous vegetables has a protective effect in breast cancer, largely attributed to sulforaphane and Indole-3-carbinol.

Sulforaphane is an isothiocyanate phytochemical from cruciferous vegetables with multiple molecular targets, anti-inflammatory, antioxidant and anti-cancer properties. Researchers have reported several chemo-prevention benefits of Sulforaphane consumption.

Several studies have demonstrated that sulforaphane influences human cancer development and progression through the modulation and/or regulation of cell cycle and key cellular mechanisms, such as reduction in tumour growth, induction of cell cycle arrest, activation of programmed cell death and disruption of signalling within the tumour microenvironment (39). In human breast cancer cells, sulforaphane has been found to inhibit cell growth, induce a G_2/M cell cycle block, increase expression of cyclin B1, induce oligonucleosomal DNA fragmentation, activate apoptosis and decrease the expression of key proteins involved in breast cancer proliferation (40-44).

Indole-3-carbinol is another phytochemical, produced by the breakdown of the glucosinolates that are found at relatively high levels in cruciferous vegetables. Indole-3-carbinol has been shown to be a potent chemo-preventative agent for hormone-dependent breast cancer through its ability to selectively induce apoptosis and alter oestrogen metabolism (45-48).

A meta-analysis of thirteen epidemiologic studies (11 case-control and 2 cohort studies) has indicated that high consumption of cruciferous vegetables was significantly associated with 15% reduction in breast cancer risk (RR=0.85, 95%CI=0.77-0.94) (49). In a more recent study involving 1,485 cases and 1,506 controls, intake of cruciferous vegetables significantly reduced the breast cancer risk by almost 50% in the Chinese population. The chemoprevention benefit of cruciferous diet is largely attributed to sulforaphane and Indole-3-carbinol (50).

In another case-control study in 1,491 patients with breast cancer and 1,482 controls, cruciferous vegetable intake was associated with a 32% reduction in breast cancer risk (highest *versus* lowest quartile OR=0.68, 95%CI=0.55-0.86, *p*-trend=0.0006). Cruciferous vegetables contain high concentrations of glucosinolates (mainly sulforaphane) that are hydrolysed by the intestinal microflora to isothiocyanates; (51). A meta-analysis of studies conducted over 18 years in Europe included a total of 3,034 of breast cancer patients and 11,492 controls showed that the multivariate odds ratio for consumption of cruciferous vegetables was significantly reduced for breast cancer (OR=0.83) (52).

Furthermore, in a case–control study involving 1,463 cases and 1,500 controls, an inverse association between consuming cruciferous vegetables and breast cancer was reported, mainly for postmenopausal women, with oestrogen receptor (ER)+ tumours [OR=0.66, 95%CI=0.50-0.86, *p*-trend=0.03] (53). Similarly, in another case–control study involving 740 Caucasian women with breast cancer and 810 controls, inverse associations were noted between consumption of cruciferous vegetables and breast cancer risk, predominantly among premenopausal women [4th quartile OR=0.6, 95%CI=0.40-1.01, *p*=0.058] (54).

Quercetin. Quercetin is a bioactive flavonoid pigment found in several fruits, vegetables and leaves. In addition to its free-radical scavenging antioxidant activity, quercetin has been reported to exert potent anti-tumoral properties.

Studies suggest that quercetin's cancer-protecting effects result from triggering TRAIL-mediated cancer cell death and targeting key signalling transducers, leading to the restoration of tumour suppressor genes and inhibition of oncogene expression (55-57). Besides, quercetin was found to reverse epigenetic alterations associated with oncogenes' activation and inactivation of tumour suppressor genes (58).

Quercetin can successfully reverse multidrug resistance and restore chemosensitivity to cyclophosphamide in human chemo-resistant triple-negative breast cancer cells (59). Also, quercetin has been found to augment doxorubicin chemotherapeutic effects against human breast cancer cells and reduce its cytotoxic side effects (doxorubicin is a first-line chemotherapeutic for breast cancer, however, its toxic side effects in normal tissues limit its clinical use) (60, 61). Quercetin may also inhibit angiogenesis in acquired tamoxifen-resistant breast cancer cells, which is a serious therapeutic problem among breast cancer patients (62).

In a meta-analysis of twelve studies (including 9,513 cases and 181,906 controls, 6 of which were prospective cohort studies, and 6 were case-control studies), the risk of breast cancer was significantly decreased by 12% in women with high intake of flavonols, including quercetin compared to those with low consumption (RR=0.88, 95%CI=0.80-0.98) (63). In a network of multicentric Italian case-control studies (10,000 cancer cases and 16,000 controls), a reduced breast cancer risk by 20% and ovarian cancer risk by 37% were reported in the cohort with a high intake of flavonols, such as quercetin (ORs for the highest vs. the lowest quintile were 0.80 and 0.63, respectively) (64, 65). Similarly, in a large Greek case-control study involving 820 women with breast cancer and 1,548 controls, an inverse association with breast cancer risk was found for consumption of flavonols in fruits, including quercetin (66). Finally, the Finnish Mobile Clinic Health Examination Survey involving a total of 10,054 individuals with 1,093 cancer cases has reported that the total cancer incidence was significantly lower with a higher consumption of quercetin (RR between the highest and lowest quartiles of quercetin intake=0.77, 95%CI=0.65-0.92, p=0.01). Breast cancer risk was also found to be lower at higher consumption of quercetin (RR=0.62, 95%CI=0.37-1.03; p=0.25). This association was even stronger when adjustment for other dietary sources were made (RR=0.54, 95%CI=0.30-0.95, p=0.14) (67).

Epigallocatechin-3-gallate (EGCG). Green tea has been extensively studied for its potential protective effect from various types of human cancers. Compared to other teas, green tea contains the highest amount of bioactive compounds that belong to the polyphenol group (68). Scientific literature has presented evidence that green tea exerts protective effects against tumorigenesis owing to its principal polyphenol, namely epigallocatechin-3-gallate (EGCG) (69).

Evidence from several laboratory studies has demonstrated the strong chemopreventive and potentially cancer chemotherapeutic effects of the major green tea constituent, epigallocatechin-3-gallate (EGCG), against breast cancer (70). Most experimental data have shown that green polyphenols can modulate multiple signalling pathways and regulate the growth, survival and metastasis of cancer cell at multiple levels (71, 72).

In addition to the inhibition of clonal expansion of cancer stem cells and the modulation of tumour progression by maintaining a quiescent state in cancer cells, green tea (EGCG) can modulate multiple cell signalling pathways implicated in angiogenesis, metastasis and invasion, such as the inhibition of matrix metalloproteinases (MMPs) and the inhibition of vascular endothelial growth factor (VEGF). EGCG has also been reported to inhibit activator protein 1 and MAPKs, cyclo-oxygenase-2 overexpression, proteasome activity, nitric oxide synthesis, HER-2/neu signalling, insulin-like growth factor-1 (IGF-1)-mediated signalling and nuclear factor-κB (NF-κB) signalling pathways. EGCG has been found to suppress the binding of epidermal growth factor (EGF) to its receptor, leading to the inhibition of EGF-mediated signal transduction pathways (73).

Moreover, previous studies have shown that green tea's major constituent (EGCG) can decrease tumorigenicity by inhibiting the formation of DNA adducts, which are alterations in DNA that result from exposure to carcinogens and affect directly the regulation of transcription of oncogenes and/or tumour suppressors (74-77). Green tea polyphenols can also down-regulate oncogenes and up-regulate tumour-suppressor genes *via* modulating multiple epigenetic events (78). Data from *in vitro* and *in vivo* studies have shown that green tea polyphenols can induce programmed cell death in breast cancer cells either by a preferential cancer-specific induction of reactive oxygen species (ROS) or by epigenetic modulation of expression of apoptosis-related genes, such as human telomerase reverse transcriptase (hTERT) (79-81).

A meta-analysis of breast cancer incidence and recurrence involving 5,617 cases of breast cancer, has shown that green tea consumption is inversely associated with the risk of breast cancer recurrence (RR_{pooled}=0.73, 95%CI=0.56-0.96). When only the case-control studies of breast cancer incidence were examined, the inverse association was maintained (RR_{pooled}=0.81, 95%CI=0.75-0.88) (82). In line with the previous meta-analysis, a more recent systematic review and meta-analysis of several observational studies encompassing 163,810 people, has reported a statistically significant inverse relationship between green tea

consumption and breast cancer risk with a reduction of risk by 15% [(OR)=0.85 (95%CI=0.80-0.92), p=0.000]. When only the case-control studies were analysed, the protective effect observed was even higher, being 19% reduction in breast cancer risk [(OR)=0.81 (95%CI=0.74-0.88), p=0.000]. The significance of case-control studies in defining the causal relationship between exposure and event cannot be overemphasised. Finally, in a sensitivity analysis of the studies with high quality scores included in this meta-analysis, the reduction of breast cancer risk reported was even higher, at 27% (83).

Omega-3 fatty acids (PUFAs). Epidemiological studies indicated that the relatively higher incidence of breast cancer in developed countries in Western Europe and North America compared to the Inuit and the Japanese can explained by the variation in dietary patterns, in particular variations concerning intake of fatty fish and fat from marine mammals, which may be key modifiers of breast cancer risk (84-86). This preventive effect towards breast cancer has been attributed to the very high dietary intake of marine polyunsaturated fatty acids (PUFAs), mainly omega-3 PUFAs (n-3 PUFA) and omega-6 PUFAs (n-6 PUFA), found in fatty cold-water fish and fat from marine mammals (87).

The protective effect of polyunsaturated fatty acids against breast carcinogenesis was supported by multiple animal experiments and *in vitro* studies (88-91). Current evidence from experimental studies has shown that ratio of n-3/n-6 PUFAs can reduce the amount of proinflammatory lipid derivatives, growth factor receptor signalling, the NF-κB mediated cytokine production, and can modulate the signal transduction mediated by the mammalian target of rapamycin (mTOR) and the growth of breast cancer cells, by competing for cyclooxygenase and lipoxygenase metabolic pathway (92). However, the precise molecular mechanism by which these marine PUFAs can affect carcinogenesis and angiogenesis of breast cancer remains to be unequivocally defined.

In order to examine the association between the risk of breast cancer and dietary n-3 PUFA intake, a meta-analysis of data from 21 independent prospective cohort studies involving 20,905 breast cancer events and 883,585 participants was performed. Higher consumption of n-3 PUFA has been reported to be associated with a 14% reduction in breast cancer risk [RR for highest vs. lowest category 0.86 (95%CI=0.78-0.94, I^2=54%)]. This relative risk was independent of whether n-3 PUFA is measured as dietary intake [RR for highest *versus* lowest category 0.85, (95%CI=0.76-0.96, I^2=67%)] or as tissue biomarkers [RR for highest *versus* lowest category 0.86, (95% CI=0.71-1.03, I^2=8%)]. The dose-response analysis showed that risk of breast cancer can decrease by a 5% per 0.1g/day increment of dietary n-3 PUFA intake (relative risk=0.95, 95%CI=0.90-1.00, I^2=52%) (93).

To quantitatively ascertain the relationship between the risk of breast cancer and high intake ratios of n-3/n-6 PUFAs, a meta-analysis of five cohort studies and six prospective nested case-control studies, involving 8,331 cases of breast cancer from 274,135 adult females from several countries was performed. Among study populations, individuals with higher dietary intake ratios of the omega-3 to omega-6 (PUFAs) were reported to have a significantly reduced risk of breast cancer (RR_{pooled}=0.90, 95%CI=0.82-0.99). When the dose-response association was analysed, an increment per 1/10 of n-3/n-6 (PUFAs) ratio in diet was associated with a further 6% reduction of breast cancer risk (RR_{pooled}=0.94, 95%CI=0.90-0.99, p for linear trend=0.012). More importantly, the subgroup analysis has shown that individuals in 3 studies from USA with higher intake ratios of n-3/n-6 in serum phospholipids had a 38% reduction of breast cancer risk (RR_{pooled}=0.62, 95%CI=0.39-0.97, I^2=0.00%; p for metaregression=0.103, p for a permutation test=0.100). When the dose-response association was evaluated as above, an increment per 1/10 of serum phospholipids of omega-3 to omega-6 (PUFAs) ratio was associated with a 27% reduction of breast cancer risk (RR_{pooled}=0.73, 95%CI=0.59-0.91, p for linear trend=0.004, p for meta-regression=0.082; p for a permutation test=0.116). As EPA and DHA cannot be synthesised *de novo* in mammals and inter-conversion between n-3 and n-6 polyunsaturated fatty acids does not exist in humans, serum phospholipids of omega-3 to omega-6 (PUFAs) ratios reflect their dietary intake ratios (94).

Alpha-linolenic acid, which is one of the most abundant omega-3 polyunsaturated fatty acid in typical Western diets, is metabolised to two long-chain n-3 PUFAs, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (95). Typical consumption of alpha-linolenic acid among Western adults is in the range of 0.5-2 g/d which is approximately 15- and 25-fold higher than of DHA and EPA, respectively (96-100). As human conversion of alpha-linolenic acid to its longer-chain derivatives EPA & DHA is inefficient, very high intakes of alpha-linolenic acid are required to allow sufficient synthesis of its longer-chain derivatives EPA & DHA (99, 101). While the total percentage of conversion of alpha-linolenic acid to EPA & DHA varies widely, ranging from 5-18.5%, it has been reported that 2.8% of dietary alpha-linolenic acid consumed is converted to EPA and that less than 1-4% of dietary alpha-linolenic acid is converted to DHA (102, 103). Furthermore, although the relationship between increased alpha-linolenic acid intake and increased EPA concentration in plasma and tissue lipids is linear, several studies revealed a tendency for DHA to decline when alpha-linolenic acid consumption is markedly increased (99). Moreover, the recent increased intake of linoleic acid, which is the main polyunsaturated fatty acid in most Western diets and is typically consumed in 5- to 20-fold greater amounts than alpha-linolenic acid, has been found to decrease tissue

concentrations of EPA and DHA (100, 104). Additionally, the choice of cooking oil and cooking method (particularly deep frying) can also qualitatively and quantitatively influence the total fatty acid content in cooked fish (6,7).

The limited conversion from dietary alpha-linolenic acid and the increased consumption of linoleic acid as well as the variation in choice of cooking method imply that protective breast tissue levels of EPA & DHA can be achieved only by direct consumption of these polyunsaturated fatty acids (105, 106). It has been evidenced that omega-3 supplementation reaches and imparts significant improvements in the ratio of n-3/n-6 PUFAs at the target breast tissue (107). This justifies a reconsideration of the dietary reference intake for EPA & DHA and provides solid and robust evidence that supports breast cancer prevention by increasing consumption of dietary intake ratios of n-3/n-6 PUFAs.

Conclusion

The protective action of particular vitamins, such as vitamin D3, folate, vitamin B6, and beta carotene, and certain dietary micronutrients, namely curcumin, piperine, sulforaphane, indole-3-carbinol, quercetin, epigallocatechin gallate (EGCG) and n-3/n-6 polyunsaturated fatty acids (PUFAs), against breast cancer *via* inhibition of proliferation, invasion, angiogenesis and metastasis is well documented. Since breast cancer is now widely recognised as an even more heterogeneous disease than ever envisioned with aberrations in diverse sets of genes, such agents with multi-targeted 'pleiotropic' effects have the potential to be chemopreventive due to their capability to inhibit multiple molecular events and signalling pathways associated with various stages of breast carcinogenesis. The limitations of epidemiological association studies related to confounding lifestyle and genetic factors pertaining to causal inferences are largely overcome by supportive evidence derived from *in vivo* and mechanistic *in vitro* studies. Therefore, a supplement that contains these micronutrients using the safest formulation and dosage should be investigated in future breast cancer chemoprevention studies and as part of standard breast cancer treatment. In the absence of such trials, which could prove challenging to conduct and analyse, it would be prudent for women, especially those at an increased risk, to consider these compounds for breast cancer chemoprevention using dietary sources or specific supplements.

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