Chapter

Micronutrient Antioxidants in the Chemoprevention of Breast Cancer and Effect on Breast Cancer Outcomes

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Abstract

Breast cancer remains one of the most frequent cancers affecting women globally. The incidence of breast cancer is rising due to improved screening and awareness, and there is epidemiological data signifying an interaction among environmental and biological risk factors in the development and progress of breast cancer. There is substantial experimental data of the protective effect of micronutrient antioxidants for breast cancer via alteration of many signaling pathways and molecular events including inducing apoptosis, and inhibition of breast cancer cell proliferation and invasion. The main focus of this review is to examine past and current epidemiological evidence that suggests that nutritional micronutrients with antioxidant properties in dietary or supplemental form may be beneficial in protecting women against breast cancer and affect outcomes.

Keywords: breast cancer, risk, antioxidants, micronutrients, mortality, recurrence, dietary, intake

1. Introduction: breast cancer

1.1 Etiology of breast cancer and role of oxidative stress

Breast cancer remains one of the most frequent cancers affecting women globally. In 2018, 2.1 million new cases were reported, accounting for approximately one in every four cases of cancer among women [1]. Breast cancer accounted for almost 15% of cancer-related deaths in women in 2018 [2]. It is more common in the developed world, with highest incidence in regions such as Europe and Northern America [1]. However, mortality rates are higher in developing regions such as Africa [1]. Breast cancer is linked to numerous risk factors including family history, gene mutations, obesity, hormonal therapy, and alcohol consumption [3] but a recognizable risk profile is not usually present in most women who develop the disease [4]. Even though

curative therapy is promising following early detection, approximately 30% of cases diagnosed at early stages will progress to metastatic disease [5]. Furthermore, cases of disseminated disease are almost always untreatable and radical prophylactic mastectomy remains the only primary preventative measure [6]. These challenges have spawned a shift in the treatment paradigm of the disease, which has led to major treatment advancements and improved palliative care. However, drug resistance and adverse side effects are common nuisances of current therapy [7]. Therefore, new approaches to breast cancer management with treatments that have minimal harmful effects and can retard tumor progression are required.

To determine effective treatment approaches for breast cancer, it may be worthwhile to elucidate the complexity of the tumor microenvironment. It has been suggested that impaired mitochondrial metabolism may be a feature of tumor progression [8]. Additionally, it has been reported that a hallmark feature of mitochondrial dysfunction is the generation of reactive oxygen species (ROS) which may cause pro-tumorigenic outcomes such as DNA damage and genomic instability [8]. Reactive oxygen species include molecules such as superoxide anion, hydrogen peroxide, hydroxyl radical and singlet oxygen. They are involved in cell signaling through second messenger pathways in both cancer cells and their normal counterparts [9]. It was reported that various cancers are characterized by overproduction of ROS that can increase pro-tumorigenic signaling, cell survival and DNA aberrations [10]. Similarly, another study reported that elevated ROS levels is necessary to support and sustain metastasis [11].

Oxidative stress is widely considered to play a major role in the initiation and pathogenesis of breast cancer [12]. It refers to the imbalance between ROS production and clearance favoring decreased clearance and a pro-oxidant environment caused by either an overproduction of ROS or decreased antioxidant activity [13]. In breast cancer, a vast majority of stromal fibroblasts becomes activated following exposure to oxidative stress resulting in hydrogen peroxide production which triggers tumorigenic changes in breast epithelial cells [12]. A plethora of high energy nutrients and growth factors are also produced which fuels metastasis [12]. Congruently, it was reported that higher levels of oxidative stress biomarkers such as malondialdehyde and oxidized glutathione were found in breast cancer patients compared to control subjects [14]. The human body comprises an antioxidant defense system which exerts its function by generating antioxidants including the catalases, glutathione peroxidases and superoxide dismutase which offer protective effects by metabolizing and scavenging free radicals to inhibit and minimize tissue damage [15]. It is important to note that despite the presence of an endogenous antioxidant system, DNA damage ensues and accumulates throughout life and could considerably contribute to the initiation and progression of cancers [16]. Given the accumulation of evidence supporting the role of ROS in the pathogenesis of breast cancer, there is a possibility that dietary micronutrient antioxidants may be useful to counteract oxidative stress induced cancer. Moreover, it was reported that antioxidant supplement use among breast cancer patients was 45–80% [17].

This paper will review information in the literature on the relationship between dietary and supplement micronutrient antioxidants including vitamins C and E and their association with the risk of breast cancer as well as outcomes such as disease recurrence and mortality.

2. Method of article selection

A literature search was conducted for all English language literature published before December 2020. The search was conducted using the electronic databases,

including PubMed, Embase, Web of Science, and Cochrane Library. The search strategy included keywords such as breast cancer, epidemiology, incidence, risk, recurrence, mortality, vitamin E, vitamin C, carotenoids, flavonoids and green tea. The authors include many interventional and observational studies that have reported findings of dietary and supplemental micronutrient antioxidants, breast cancer incidence, and progression. The majority of these studies focused on vitamins E and C, carotenoids, specifically beta- and alpha-carotene, lycopene as well as the flavonoids, flavonols and isoflavones.

3. Epidemiological evidence of vitamins as antioxidants

3.1 Vitamin C

3.1.1 Vitamin C and breast cancer risk

Vitamin C is a naturally occurring essential micronutrient that is soluble in water and its antioxidant properties involve neutralizing reactive oxygen species as well as other free radicals [18]. Investigational experiments and epidemiologic findings on vitamin C and breast cancer risk are still inconclusive and reviews of data have suggested both detrimental and protective effects on overall risk of breast cancer [19]. Prospective studies on vitamin C intake and breast cancer risk have yielded diverse findings [20–23]. A recent meta-analysis reported that dietary vitamin C but not supplements was associated with a lesser risk of breast cancer incidence (RR = 0.89; 95% CI: 0.82–0.96) [20]. In the European Prospective Investigation into Cancer and Nutrition Study of 7,502 primary invasive breast cancer cases with a median follow-up time of approximately 9 years, multivariate analyses showed that vitamin E and C were not related with breast cancer risk in postmenopausal and premenopausal women. However, high intake of vitamin C was associated with decreased breast cancer risk in postmenopausal women utilizing exogenous hormones [21]. Earlier, in the Netherlands Cohort Study comprising of 62,573 women with 650 incident breast cancer cases identified after a follow-up of 4.3 years, dietary Vitamin E and vitamin C supplement use did not influence breast cancer risk, but there a small reduction in risk with increasing dietary intake of vitamin C particularly at the highest quintile [22]. Correspondingly, findings from the Women's Health Initiative Observational Study which followed 84,805 women for approximately 8 years with 2,879 incident invasive cancer cases ascertained, showed a weak positive association of breast cancer risk with total and supplemental vitamin C particularly among postmenopausal women (**Table 1**) [23].

Other prospective studies showed increased breast cancer risk with dietary or supplemental vitamin C. Using a large cohort of 2,482 invasive breast cancer cases in 57,403 postmenopausal Women, Cadeau et al. examine the association between vitamin C supplement use and breast cancer risk while bearing in mind dietary vitamin C intake, and found no relation with the overall risk, but females in the fourth quartile of vitamin C intake from foods had a 32% increase in breast cancer risk [24]. Published in 2011, a meta-analysis of 51 studies comparing highest with the lowest vitamin C intake from supplements may be associated with higher breast cancer risk [25], but it was noted that the overall result was influenced by a single large study [23]. In this same meta-analysis, dietary and total vitamin E, and dietary vitamin A significantly decreased breast cancer risk for cohort studies, but the results became nonsignificant when case–controlled studies were pooled [25]. Notably, Sharhar et al. examined relations between oxidative stress and antioxidant status in 57 newly diagnosed breast cancer cases and found poor antioxidant status

Vitamin/ Micro-nutrient (antioxidant)	Reference	Study design	Population (Case, participants)	Exposure	Risk estimates (95% CI)	Outcome
Vitamin C and E	29	Case–control	297 breast cancer cases and 311 controls	Dietary vitamin C	Vitamin C: OR = 0.53 (0.33–0.86) Vitamin E: OR = 0.55 (0.34–0.88)	Reduction by 47% (mainly in premenopausal women) Reduction by 45%
Lycopene	150	Case–control	46 breast cancer cases and 63 controls	Lycopene in adipose tissue	OR = 0.32 (0.11–0.94)	Reduction by 68%
Vitamin E	29	Case–control	297 breast cancer cases and 311 controls	Dietary vitamin E	OR = 0.55 (0.34–0.88)	Reduction by 45%
Vitamin E	53	Population-based case–control	2,362 breast cancer cases and 2,462 controls	Vitamin E (supplement)	OR = 0.75 (0.58–0.97)	Reduction by 25%
Alpha-carotene and beta-carotene	90	Population-based case–control	5,707 women with incident invasive breast cancer	Alpha-carotene and beta-carotene (supplement)	Alpha-carotene OR = 0.82 (0.68–0.98; P_{trend} = 0.07) Beta-carotene OR = 0.81 (0.68–0.98; Ptrend = 0.009)	Reduction by 18% for premenopausal women Reduction by 19% for premenopausal women
Alpha-carotene and beta-carotene	23	Women's Health Initiative Observational Study	84,805 women followed for average 7.6 yrs.	Alpha-carotene and beta-carotene (supplement)	Alpha-carotene RR = 0.83 (0.70–0.99, P_{trend} = 0.019). Beta-carotene RR = 0.78 (0.66–0.94, P_{trend} = 0.021)	Reduction by 17% (highest vs. lowest quintile) Reduction by 22% (highest vs. lowest quintile)

Vitamin/ Micro-nutrient (antioxidant)	Reference	Study design	Population (Case, participants)	Exposure	Risk estimates (95% CI)	Outcome
Total flavonoids and flavonols	110	Case–control	1522 breast cancer cases and 1547 controls	Dietary total flavonoids and flavonols	Total flavonoids: OR = 0.66 (0.54–0.82) Flavonols: OR = 0.51 (0.41–0.63)	Reduction by 34% Reduction by 49%
Flavones and flavonols	112	Case–control	1,434 breast cancer cases and 1,440 controls	Dietary flavones and flavonols	Flavones: OR = 0.61, (0.45–0.83) Flavonols: OR = 0.54 (0.40–0.73)	Reduction by 39% Reduction by 46%
Soy isoflavones	129	The Shanghai Breast Cancer Survival Study (prospective)	4,139 stage 0 –III breast cancer patients and 1987 pre–/ perimenopausal and 2152 postmenopausal patients	Dietary soy isoflavones	HR = 0.22, (0.09–0.53)	Reduction by 78% in premenopausal women (high intake)
Lycopene and beta-carotene	93	Case–control	122 breast cancer cases and 632 healthy controls	Dietary lycopene and beta-carotene	Lycopene: Adjusted OR = 0.26, (0.14–0.46) Beta-carotene: Adjusted OR = 0.43 (0.23–0.82)	Reduction by 74% Reduction by 57%

Table 1.
Summary of selected studies that provide risk estimates of the associations between dietary and supplemental vitamins and micronutrients (antioxidants) and breast cancer risk.

as indicated by low plasma vitamin C which elevated by two to three times the breast cancer risk [26].

The findings of reduced breast cancer incidence with vitamin C consumption was more evident in case–control studies. In Nurses' Health Study involving a large cohort of 83,234 women where 2,697 incident cases of invasive breast cancer was identified after 14 years, the associations between vitamins A, C and E, fruit and vegetables, and specific carotenoids and breast cancer risk were examined. There was a weakly inverse association between dietary vitamin A and breast cancer risk in premenopausal women and strong inverse association with increasing quartiles of dietary vitamin C, alpha-carotene and beta-carotene among premenopausal women who had a positive family history of breast cancer [27]. Likewise, a case–control study conducted in Korea comprising 224 incident breast cancer cases and 250 matched controls establish that vitamin C and beta-carotene intake were associated with decreased breast cancer risk, thus possibly lowered incidence in Korean women [28]. Moreover, in an earlier case–control study of 297 breast cancer cases matched with 311 control subjects, there was a significant reduction in breast cancer risk with beta-carotene, alpha-tocopherol and vitamin C when the lowest quartile was used as reference and odds ratios adjusted for the highest quartile [29] (**Table 1**). Conversely, no evidence of association between dietary or total vitamin C intake and breast cancer risk in the UK Dietary Cohort Consortium pooled analysis involving a nested case–control study [30], nor between dietary and supplement vitamin C intake and breast cancer risk in a large prospective study of 89,494 women during eight years of follow-up [31].

3.1.2 Vitamin C and survival outcomes

Cancer chemoprevention in vitro studies have demonstrated that vitamin C in pharmacological concentrations is cytotoxic to numerous type of cancer cells including ovarian and pancreatic while not affecting normal cells [32].

Globally, there is increasing use of vitamins among cancer patients and in the UK Women's Cohort Study comprising 12,453 females, there was self-reported frequently high dose vitamin C supplement intake use among breast cancer patients [33]. Furthermore, a number of epidemiologic studies have investigated the association between dietary vitamin C, vitamin C supplements and survival outcomes subsequent to breast cancer diagnosis. In a meta-analysis of prospective studies, post-diagnosis vitamin C supplement use was associated with decreased risk for breast cancer-specific (RR = 0.85, 95%CI: 0.74–0.99) and total mortality (RR = 0.81, 95%CI: 0.72–0.91) while dietary intake was also statistically significant for these two survival outcomes [34]. It was noted that in the Swedish Mammography Cohort Study comprising of 3,405 females with invasive breast cancer there was a marginal significant association between dietary vitamin C intake and all-cause mortality, but no association between supplement use subsequent to diagnosis and breast cancer-specific mortality [35].

Nevertheless, the findings are not consistent with intake of dietary vitamin C stated to decrease mortality risk in some studies [36, 37], while no relation in other epidemiologic studies [38–40]. There are also other prospective studies, which have investigated the relationship between vitamin C supplement use and breast cancer survival [17, 41, 42], and recently there is a published meta-analysis of observational studies [20]. In this meta-analysis, pooled results from 69 studies, the hazard risk for all-cause mortality was 0.82 (95% CI: 0.74–0.91), breast cancer recurrence 0.81 (95% CI: 0.67–0.99) and breast cancer-specific mortality 0.78 (95% CI: 0.69–0.88) [20].

3.1.3 Vitamin C use during chemotherapy and radiation therapy

There are apprehensions that supplement use, mainly antioxidants might decrease the cytotoxicity of chemotherapy and make it less operative [43]. Dietary antioxidant supplementation with radiation treatment and conventional chemotherapy have yielded conflicting results and many randomized clinical trials have reported deceased therapy-related side effects [44, 45]. There is data that attest to the protective effect of tumor cells as well as healthy cells by antioxidants since they neutralize reactive oxygen species and other free radical generated by some forms of chemotherapy and radiotherapy, thus reducing efficacy and ultimately survival [46, 47]. In the Breast Cancer Enrolled in a Cooperative Group Clinical Trial (SWOG S0221), Ambrosone et al. assessed associations between dietary antioxidant supplement (vitamins C, E and A as well as coenzyme Q and carotenoids) before and during chemotherapy (doxorubicin, paclitaxel and cyclophosphamide) treatment and survival outcomes. The use of any of the dietary supplements such as vitamin C resulted in a 41% higher hazard of recurrence of marginal significance, with a comparative but lesser association with mortality [48]. The authors suggested that patients should exercise caution when contemplating the use of supplement vitamin C during chemotherapy [48].

Conversely, epidemiologic studies have demonstrated improved usefulness of numerous cancer therapeutic agents with less adverse side effects when administered concomitantly with antioxidants [49]. Interesting, in a recent study it was found that vitamin C increased the therapeutic window of bromodomain and extra-terminal inhibitors thereby improving their efficacy for treating patients with aggressive triple negative breast cancer [50].

3.2 Vitamin E

3.2.1 Vitamin E and breast cancer risk

The role of dietary and vitamin E supplements in preventing breast cancer still remains unclear [51]. Previous research have demonstrated that there is a lack of any consistent association between vitamin E and the risk of breast cancer [52]. In a large population-based case–control study conducted in Canada that examined antioxidants intakes from diet and supplements and their potential breast cancer risk, 10 years or more supplementation with vitamin E was associated with reduced breast cancer risk (OR = 0.75, 95% CI: 0.58–0.97). However, no significant effect of dietary vitamin E intake or from supplementation less than 10 years was observed [53] (**Table 1**). Likewise, Fulan et al. conducted a meta-analysis of 51 studies on vitamin E intake and found that dietary vitamin E significantly decreased breast cancer risk, but there was no significant dose–response relationship in the higher intake of vitamin E [25]. An earlier case–control study comprising 297 breast cancer cases and 311 control subjects conducted in the United States found a significant reduction in breast cancer risk associated with high intake of dietary vitamin E (OR = 0.55; 95% CI: 0.34–0.88). However, no association was observed between vitamin E supplement intake and breast cancer risk [29]. Notably, findings from the Shanghai Breast Cancer Study suggests that vitamin E supplements may confer safeguard against breast cancer (OR = 0.80; 95%CI, 0.60–1.00) among Chinese women who had low dietary intake [54]. In addition, there were other studies that corroborated these finding including an inverse association of dietary vitamin E with breast cancer risk in a hospital-based case–control study of Chinese women [55] and vitamin E significantly decreased breast cancer risk in a case–control study comprising Greek women [56].

However, there are a number of prospective and case–control studies that reported no association between dietary and/or supplement vitamin E intake and breast cancer risk [22, 31, 57]. Verhoeven et al. reported findings from the Netherlands Cohort Study, a large prospective cohort research that examined the relationships between various vitamins, vegetables and fruits with breast cancer risk and found no strong evidence of dietary vitamin E intake in the etiology of breast cancer [22]. An earlier large prospective study found that large intake of dietary vitamin E did not protect from breast cancer (OR = 0.99, 95%CI: 0.83–1.19) [31]. Results from other studies on dietary or supplemental vitamin E intake demonstrated similar null association [58, 59]. These include: a case–control by Wang et al. that did not find any meaningful association of dietary vitamin E intake with breast cancer risk [60], no association of higher dietary intake of vitamin E (in early adult life) among postmenopausal women in the Nurses' Health Study II [57], and meta-analysis of 26 studies that found no effect of vitamin E supplementation on breast cancer risk on reviewing data from five cohort and four case–control studies [61].

3.2.2 Vitamin E use during chemotherapy and radiation therapy

Over the last decade the use of antioxidant supplements after breast cancer diagnosis and during treatment significantly increased and has become quite common among survivors [53, 61]. In a review of the literature on non-herbal nutrition supplements use in relieving symptoms induced by chemotherapy or radiation treatment, Samuels et al. showed that a number of studies suggest that antioxidant supplements use comprising glutamine, vitamin E and acetyl-L-carnithine possibly might decrease the occurrence and severity of paclitaxel-induced neuropathy [62]. In a comprehensive review of the 22 prospective studies by Greenlee et al. in 2009 that examined the association between use of antioxidant supplements (vitamin E as well as multivitamins, vitamin C, antioxidant combinations, soy isoflavones, melatonin, glutathione, or glutamine) and patient outcomes, there were no single antioxidant supplement during conventional breast cancer therapy that had a significant effect on recurrence, tumor response, toxicities, or survival. The authors indicated that findings from limited studies proposed that vitamin E decrease the hot flashes in patients treated with hormonal therapy and glutamine for oral mucositis [17]. In a more recent study, Huang et al. assessed the associations of dietary intake of fish, fruit and vegetable supplemented with vitamins E and B, and post-therapy cognitive recovery in 1,047 patients with breast cancer enrolled in the Shanghai Breast Cancer Survival Study. Higher dietary intake and supplement use were associated with greater cognitive scores at 36 months post-diagnosis thus improvement in post-therapy mental recovery [63].

3.2.3 Vitamin E and survival outcomes

Globally, the consumption of dietary supplements including vitamins and multivitamins/multi-minerals is increasing more so among females than males [64, 65]. However, there are only few studies that have examined vitamin E supplementation and survival outcomes in breast cancer patients. A well-designed prospective population-based prospective cohort study comprised of 4,877 females diagnosed with invasive breast cancer in China reported that vitamin E as well as multivitamin use were beneficial in improving survival and mortality rates. There was a 22% decreased recurrence risk and 18% lower mortality risk in females who use vitamin E supplement within 6 months after breast cancer diagnosis [42] (**Table 2**). Likewise, in the Life After Cancer Epidemiology (LACE) Study

comprising of 2,264 females with early-stage breast cancer, 81% use antioxidants post-diagnosis. The regular use of vitamin E was concomitant with reduced risk of disease recurrence (HR = 0.71, 95%CI: 0.54–0.94) and diminished risk for all-cause mortality (HR = 0.76, 95%CI: 0.58–1.00) [41] (**Table 2**). Similarly, data from the After Breast Cancer Pooling Project showed that vitamin E was associated with reduced risk of breast cancer recurrence (RR = 0.88; 95%CI 0.79–0.99) [66]. The findings of a case–control study comprising 385 post-menopausal breast cancer patients performed in the United States corroborated previous reports as the use of antioxidant supplement (vitamins E or C, selenium or β-carotene) was associated with decreased breast cancer-specific death [37]. While these results suggest that antioxidants supplement use may have a protective effect and improve breast cancer survival, there were concerns of recall bias and the legitimacy of the exposure assessment. Furthermore, a recent systematic review and meta-analysis comprising randomized clinical trials and observational studies showed that vitamin E significantly reduced total mortality (RR = 0.76, 95% CI: 0.64–0.90) and breast cancer recurrence (RR = 0.69, 95% CI: 0.55–0.85) [67] (**Table 3**).

3.3 Multivitamins

3.3.1 Multivitamins use during chemotherapy and radiation therapy

Despite over thirty years of research examining dietary antioxidant supplement use during radiation therapy and conservative chemotherapy, there are significant disagreements regarding the effectiveness of this complementary therapy [68, 69]. Encouraging results from many randomized control trials confirmed that the concomitant administration of supplementation antioxidants with radiation therapy and chemotherapy decreases side effects related to treatment [70]. However, some studies have suggested that antioxidant supplementation may guard malignant tumor cells from the pro-oxidant effects such as oxidative injury produced by chemotherapeutic agents and radiation treatment [71, 72].

The quality of life and performance of normal daily activities can be negatively impacted by chemotherapy-induced peripheral neuropathy [73]. Using data from the Diet, Exercise, Lifestyle, and Cancer Prognosis (DELCaP) study, Zirpoli et al. reported that the use of multivitamins prior to diagnosis was associated with decreased symptoms of chemotherapy-induced peripheral neuropathy while use during therapy was slightly related with this outcome [74]. However, in a recent study, Jung et al. reported findings from the population-based Mamma Carcinoma Risk Factor Investigation (MARIE) study and noted that pre and post-diagnosis supplement use among of 2,223 postmenopausal women diagnosed with non-metastatic breast cancer was 36% and 45% respectively. The use of antioxidants throughout radiation therapy and chemotherapy was associated with higher total mortality risk (HR = 1.64; 95% CI: 1.01–2.66) and exacerbated recurrence-free survival (HR = 1.84; 95% CI: 1.26–2.68) [75]. The was also no relations between post-diagnosis use of supplement and disease prognosis, and the authors suggests that breast cancer patients should not use antioxidants during radiation therapy and chemotherapy [75].

3.3.2 Multivitamins and survival outcomes

The natural activity of dietary and supplement antioxidants is due to a number of factors comprising the existing level of oxidative stress, collaborations of antioxidants, and the level of antioxidants present in cells [45]. The consumption of vitamin supplements among breast cancer patients post-diagnosis is quite common [76]. There are prospective studies that have demonstrated that multivitamin

Vitamin/ Micro-nutrient (antioxidant)	Reference	Study design	Population (Case, participants)	Exposure	Risk estimates (95% CI)	Outcome
Vitamin E, C and multivitamins	42	Population-based prospective cohort	4,877 women diagnosed with breast cancer (aged 20–75 yrs)	Vitamin E, C and multivitamins	HR = 0.82 (0.65–1.02) for mortality HR = 0.78 (0.63–0.95) for risk of breast recurrence	Reduction by 18% and 22% respectively
Vitamin E and C	41	Life After Cancer Epidemiology (LACE) cohort	2,264 women with early stage breast cancer	Vitamin E and C (supplement)	(i) Vitamin E: HR = 0.71 (0.54–0.94) for breast cancer recurrence and HR = 0.76 (0.58–1.00) for all-cause mortality Vitamin C: HR = 0.73 (0.55–0.97) for risk of breast cancer recurrence	Reduction by 29% and 24% respectively Reduction by 27%
Vitamin C and E	66	After Breast Cancer Pooling Project	Four cohorts of 12,019 breast cancer survivors	Vitamin C and E (supplement)	Vitamin C: RR = 0.81 (0.55–0.97) for all-cause mortality Vitamin E: RR = 0.88 (0.79–0.99) for risk of breast cancer recurrence	Reduction by 19% Reduction by 12%
Soy isoflavones or soy protein	143	The Shanghai Breast Cancer Survival Study (a large, population-based cohort	5,042 female breast cancer survivors	Soy isoflavones or soy protein intake	HR = 0.68 (0.64–0.87) for risk of breast cancer recurrence (HR = 0.71 (0.54–0.92) for all-cause mortality (ER+ or ER- women)	Reduction by 32% Reduction by 29%
Soy isoflavonones	144	Prospective	256 Chines women		Soy isoflavones: OR = 0.25 (0.09–0.54) for breast cancer mortality	Reduction by 75%

Table 2.
Summary of selected studies that provide risk estimates of the associations between dietary and supplemental vitamins and micronutrients (antioxidants) and breast cancer outcomes such as recurrence and mortality.

Vitamin/ Micro-nutrient (antioxidant)	Reference	Study design	Population (Case, participants)	Exposure	Risk estimates (95% CI)	Outcome
Vitamin C	20	Meta-analysis	69 studies relevant to breast cancer risk (54 studies) and survival (15 studies)	Dietary vitamin C	RR = 0.78 (0.69–0.88) for breast cancer-specific mortality; RR = 0.81 (0.67–0.99) for risk of breast cancer recurrence	Reduction by 22% and 19% respectively
Vitamin C	34	Meta-analysis	10 studies	Supplement vitamin C	RR = 0.81 (0.72–0.91) for total mortality & RR = 0.85 (0.74–0.99) for risk of breast cancer-specific mortality	Reduction by 19% and 15% respectively
Vitamin C and E	67	Meta-analysis	Observational studies and randomized clinical trials	Vitamin C and E (supplement)	Vitamin C: RR = 0.79 (0.68–0.92) for total mortality and RR = 0.76 (0.64–0.91) for risk of breast cancer recurrence Vitamin E: RR = 0.76 (0.64–0.90) for total mortality and RR = 0.69 (0.55–0.85) for risk of breast cancer recurrence	Reduction by 21% and 24% respectively Reduction by 24% and 31% respectively
Alpha carotene and beta-carotene	91	Meta-analysis	33 observational studies	Dietary alpha carotene and beta-carotene	Alpha-carotene: RR_{pooled} = 0.91 (0.85–0.8, P = 0.01) for breast cancer risk Beta-carotene RR_{pooled} = 0.94 (0.88–1.00, P = 0.05)for breast cancer risk	Reduction by 9% Reduction by 6%
Soy isoflavones	135	Meta-analysis	35	Soy flavones intake	Premenopausal: OR = 0.59 (0.48–0.69) for breast cancer risk Postmenopausal women: OR = 0.59, (0.44–0.74) for breast cancer risk particularly in Asian women	Reduction by 41% Reduction by 41%
Soy isoflavones	146	Meta-analysis	18 studies	Soy isoflavones intake	RR = 0.89 (0.79–0.99) for risk of breast cancer incidence RR = 0.84 (0.70–0. 99) for risk of breast cancer recurrence	Reduction by 11% Reduction by 16%

Vitamin/ Micro-nutrient (antioxidant)	Reference	Study design	Population (Case, participants)	Exposure	Risk estimates (95% CI)	Outcome
Lutein/zeaxanthin	151	Meta-analysis	8 cohort studies	Lutein/zeaxanthin	RR = 0.84 (0.70–1.01, P_{trend} = 0.05)	Reduction by 16%
Quercetin	116	Meta-analysis	12 studies (6 prospective cohort and 6 case controls)	Quercetin intake	RR = 0.88 (0.80–0.98)	Reduction by 12%

Table 3.
Summary of selected meta-analysis and systematic reviews that provide risk estimates of the associations between dietary and supplemental vitamins and micronutrients (antioxidants) and breast cancer risk.

consumption improve survival rates in breast cancer patients [66, 77]. In the After Breast Cancer Pooling Project, Poole et al. examined the associations between post-diagnosis supplement use (multivitamins, vitamin E, D, C and B) and survival outcomes such as breast cancer-specific mortality, total disease mortality and risk of breast cancer recurrence in four cohorts of 12,019 patients in China and the United States. Using multivariate models, antioxidant supplement use (multivitamins, vitamin E or, C) was associated with improved survival as there was a 16% reduced risk of total mortality but not related with disease recurrence [66]. The findings of the Life After Cancer Epidemiology study that comprised of 2,236 women diagnosed with early-stage breast cancer indicate that multivitamin use may be valuable in improving breast cancer outcomes as frequent use prior to and after diagnosis was associated with non-significant reduced death from any cause and disease recurrence. In addition, the protective effect was for only breast cancer survivors treated by both radiation and chemotherapy, and radiation only and those who ate more fruits and vegetable and engaged in physical exercise had improved overall survival [77]. Notably, a recent systematic review and meta-analysis comprising randomized clinical trials and observational studies reported that multivitamin use lower breast cancer recurrence, and these findings were mostly based on observational studies while more randomized clinical trials are required to justify any recommendation for the dietary supplement use [67].

Conversely, in a large retrospective cohort study of breast cancer patients belonging to the British Columbia Cancer Agency followed for 68 months, an administered regimen mega-dose vitamin/mineral supplements non-significantly increase the hazard ratios for disease-free survival and breast cancer-specific mortality. However, limitations include absence of critical information on use of over-the-counter vitamins, treatment compliance and possible selection bias [78]. Moreover, in a multicenter study of 3,081 early-stage breast cancer patients, although dietary supplement users had acceptable intakes of micronutrients, vitamin use and mineral intake was not concomitant with all-cause mortality.

4. Epidemiological evidence of carotenoids as antioxidants

4.1 Fruit, vegetables and breast cancer risk

Epidemiologic studies have suggested that increased fruit and vegetable intake is associated with lower risk of breast cancer [79]. Supporting evidence is provided by findings from a pooled analysis of eight prospective cohort studies where total fruit and vegetable intake was associated with decreased breast cancer risk (RR = 0.93, 95% CI: 0.86–1.00; P_{trend} = 0.12) when comparing the highest with the lowest quartiles [80]. Recent systemic review and meta-analysis indicated that high intakes of vegetables and fruits were associated with lower risks of breast cancer [81, 82], while a large-scale study demonstrated that the same may be related with improved overall survival among primary breast cancer patients [83]. However, a large prospective study such as the European Prospective Investigation into Cancer and Nutrition did not find a relationship between fruit and vegetable intake, and breast cancer risk [84].

4.2 Carotenoids

4.2.1 Alpha-carotene, beta-carotene intake and breast cancer risk

Carotenoids such as alpha-carotene, beta-carotene, lycopene and beta-cryptoxanthin are found in fruits and in dark green leafy vegetables as well as in yellow

and orange vegetables [85]. The chemo-prevention and protective potential of carotenoids lies in their antioxidant, retinoic and anti-proliferative activities and obstructing estrogen signaling of 17β-estradiol, with subsequent weakening of the properties of malignancies such as breast cancer that are hormone-dependent [86]. There are a number of studies that have examined the relation of breast cancer risk with dietary and/or supplemental consumption of carotenoids [87–89]. In a large population-based case–control study consisting of 5,707 women with incident invasive breast cancer (3,516 postmenopausal women and 2,363 premenopausal women), there were inverse associations observed among premenopausal women for high levels of alpha-carotene (OR = 0.82, 95% CI: 0.68–0.98) and beta-carotene (OR = 0.81, 95% CI: 0.68–0.98) but not for postmenopausal women [90] (**Table 1**). Likewise, in the Women's Health Initiative Observational Study, high dietary beta-carotene intake (RR = 0.78; 95% CI: 0.66–0.94; P_{trend} = 0.021) and elevated alpha-carotene (RR = 0.83; 95% CI: = 0.70–0.99; P_{trend} = 0.019) were inversely related to risk of estrogen receptor (ER)-positive and progesterone receptor (PR)-positive breast cancer. However, supplemental or total beta-carotene were not related to breast cancers demarcated by PR and ER status [23]. In an earlier population-based case–control study conducted in Canada, Nkondjock et al. found decreased risk for beta-carotene for those who never used hormone replacement therapy [89] but increased breast cancer risk associated with significantly high serum levels of alpha-carotene (OR = 2.40; 95% CI: 0.90–6.41) in premenopausal women.

These findings were corroborated by a review study that systematically summarized the associations between beta-carotene and alpha-carotene, and breast cancer risk. In the meta-analysis that comprehensively review the associations between carotenoids and breast cancer, higher intakes of dietary beta-carotene significantly decreased breast cancer risk by 6.0% (RR_{pooled} = 0.94; 95% CI: 0.88–1.00) and dietary alpha-carotene lower the risk by 9.0% when the cohort studies were pooled. Furthermore, significant dose–response associations were seen in both the higher intake of dietary and total beta-carotene with decreased breast cancer risk when considering cohort studies and case–control studies [91] (**Table 3**). There are other observational studies that have confirmed an inverse relationship of dietary or supplemental alpha-carotene or beta-carotene with risk of breast cancer [27, 87, 92, 93].

However, there are few studies that have reported null association between the carotenoids and breast cancer risk [84, 88, 94]. Terry et al. found no clear association between alpha-carotene and beta-carotene, and breast cancer risk in a large cohort of women who were registered in the Canadian National Breast Screening Study [88]. In subsequently large prospective study of women enrolled in the European Prospective Investigation Into Cancer and Nutrition there was no association of dietary beta-carotene with breast cancer risk, although beta-carotene supplement demonstrated a protective effect against lobular breast cancer (IRR = 0.72; 95%CI: 0.57–0.91] [84]. This study also found no association between overall breast cancer and any micronutrients, while some effects were shown when stratifying by breast cancer subtypes [84]. Finally, there is another study that have reported null association between the carotenoids and breast cancer risk [95].

4.2.2 Serum and plasma levels of carotenoids (alpha-carotene, beta-carotene) and breast cancer risk

Blood vitamin intakes are regarded as biomarkers of the consumption of vegetables and fruits [96]. Plasma or serum levels of antioxidants such as vitamin E are thought to be related to breast cancer risk but results from prospective and case control studies remain inconclusive [97]. In a nested case–control study comprising

1,502 incident breast cancer cases and 1,502 controls within the European Prospective Investigation into Cancer and Nutrition cohort, plasma vitamin E level was not statistically associated with ER negative or ER positive breast cancer [98]. Epplein et al. earlier published a nested case–control study, a sub-cohort of the Multiethnic Cohort Study which demonstrated that multiethnic women with breast cancer were more likely to have lower levels of vitamin E than matched controls [99]. Notably, a meta-analysis of 40 studies by Hu et al. summarize the associations between plasma levels of vitamins A, C and E, and breast cancer risk and observed significant relationship between plasma vitamin E levels and breast cancer incidence (OR_{pooled} = 0.42, 95% CI: 0.25–0.72, p = 0.001). The authors suggested that severe vitamin E could increase breast cancer risk [100]. Furthermore, even though there was an association between serum vitamin E [biomarker of fruit and vegetable intake, (OR = 0.68, 95% CI: 0.41–1.10)] in the E3N-EPIC Study, it was not statistically significant (P_{trend} = 0.26) [101].

However, there are findings from studies that do not support plasma or serum levels of vitamin E being associated with reduced risk of breast cancer [54, 102]. In a nested case–control comprising of 365 incident breast cancer cases and 726 individually matched control women within the prospective population-based Shanghai Women's Health Study, there was no association between plasma levels of vitamin E and reduced breast cancer risk, although the authors noted that there may be protective effects among sub-groups of women [54]. Likewise, in an earlier case–control study nested in a prospective cohort from the Breast Cancer Serum Bank in Missouri, United States no evidence of the protective effect of vitamin E was observed for breast cancer, although carotenoids such as lycopene and beta-cryptoxanthin may protect against breast cancer [103]. There are other studies that have reported null findings in the relationship between serum or plasma levels of vitamin E and breast cancer risk [102, 104]. These include: no association between plasma vitamin E levels and breast cancer risk in the Nurses' Health Study [105] and no significant association of plasma vitamin E levels in a nested case-referent study conducted in Sweden [106].

5. Epidemiological evidence of flavonoids as antioxidants

5.1 Flavonols and breast cancer risk

Flavonoids are an assembly of naturally occurring phenolic compounds located in vegetables and fruits and are classified into 6 main sub-classes based on the complexity of their structure. They include flavanones, flavones, flavonols, flavan-3-ols, isoflavanones and anthocyanins [107]. Investigational studies have suggested that flavonoids such as flavonols, flavones and flavanones possess preventative biological activity on breast carcinogenesis and is protective against commencement and development of tumor [108]. Nevertheless, epidemiological data regarding the associations between these flavonoid biomarkers and risk of breast cancer is inadequate and is very much needed to evaluate the definite effects of flavonoids in humans [109].

There is epidemiological evidence determined by prospective cohort study and case-study designs that have suggested an associations between dietary and supplemental flavonoids intake and breast cancer risk [110, 111]. In a recent case–control study that examined the relationship between breast cancer risk and total and subclasses of flavonoids, higher dietary intakes of total flavonoids (OR = 0.66, 95% CI: 0.54–0.82), flavonols (OR = 0.51, 95% CI: 0.41–0.63) were inversely associated with breast cancer risk [110] (**Table 1**). No significant relationship was observed

between the flavins, flavan-3-ol monomers and flavanols, and breast cancer risk [110]. These findings are compatible with those of a large case–control study conducted in Italy, where decreased breast cancer risk was found for flavonols (OR = 0.80, P_{trend} 0.06) and flavones (OR = 0.81, P_{trend} = 0.02), but not for flavan-3-ols, flavanones, isoflavones and anthocyanidins [111]. Similarly, in a subsequent case–control study of United States women reduced breast cancer risk was related with high dietary uptake of flavones (OR = 0.61, 95% CI: 0.45, 0.83), flavonols (OR = 0.54, 95% CI: 0.40–0.73) and flavan-3-ols in postmenopausal women. The authors suggested that consuming sufficient amount of these flavonoids could be beneficial to these women in the chemoprevention of breast cancer [112] (**Table 1**). Notably, in a recent hospital-based case–control, higher levels of serum flavonols (OR = 0.52, 95% CI 0.38–0.70) and flavanone (OR = 0.45, 95% CI: 0.34–0.60) were significantly associated with decreased breast cancer risk [113]. The outcomes of these studies corroborated those of other case–control studies [114, 115] which supported the protective influence of high dietary intake of flavonols and flavones against breast cancer particularly among postmenopausal females.

The findings from prospective cohort studies are not so favorable regarding the chemo-preventative actions of flavonoids. In a meta-analysis of epidemiologic studies comprising 6 prospective cohort and 6 case–control studies, higher dietary intake of flavones (RR = 0.83, 95% CI: 0.76–0.91), flavonols (RR = 0.88, 95% CI: 0.80–0.98) decreased breast cancer risk although there were no significant relation of flavanones, flavan-3-ols and anthocyanins particularly in post-menopausal women [116] (**Table 3**). However, The Nurses' Health Study II investigated the effect of dietary flavonols on breast cancer risk, and found a non-significant null association with a risk ratio of 0.94 (95% CI: 0.72–1.22, P_{trend} = 0.54) that was reported for flavonol-rich foods. Furthermore, dietary intakes of flavonol containing foods such as beans and lentils were inversely associated with breast cancer risk but this was not observed for onions, apples, blueberries tea, green pepper and broccoli [117]. There was also no association and thus no protective effects against breast cancer risk for increased intake of flavanones [118–120], flavanols [118, 119], flavonols [118–120], flavones [118], anthocyanidins [118] as well as total flavonoids [118–122].

5.2 Soy isoflavones and breast cancer risk

Isoflavones are a subclass of flavonoids and are found in legumes such as soybeans and soy products. These polyphenolic compounds are derived from plants and the three main isoflavones are daidzin, glycitin and genistin [123]. Globally the consumption of soy and soy products is increasing as the health benefits due to their biological actions including estrogenic and anti-estrogenic properties, inhibition of tumor proliferation, antioxidant, anti-inflammatory and lower risk for cardiovascular disease [124, 125]. Notwithstanding potential mechanisms from experimental studies, epidemiological evidence from case–control and prospective cohort studies regarding association of soy food and isoflavone, and breast cancer risk provide unreliable results [126–128].

In The Shanghai Breast Cancer Survival Study that assessed bone fracture incidence and its relationship with soy food consumption among breast cancer patients, high soy isoflavone intake was concomitant with decreased risk among both peri- and premenopausal subjects (HR = 0.22, 95% CI: 0.09–0.53) but no association for postmenopausal subjects [129] (**Table 1**). Similarly, a recent study that examined the relationship between isoflavone intake and hereditary breast cancer risk, reported that high intake of this flavonoid was inversely related with luminal A breast cancer hazard in women who are BRCA2 mutation carriers [130]. Conversely,

in a large prospective study comprising women from the Epidemiologique aupres de Femmes de la Mutuelle Generale de l'Education Nationale (E3N) cohort, there was no relation between past consumption of soy isoflavones supplement and breast cancer risk (HR = 1.36, 95% CI: 0.95–1.93) particularly among premenopausal patients [131]. Furthermore, in this study, there were contrasting associations of soy supplements with estrogen receptor-positive (HR = 0.78, 95%CI: 0.60–0.99) and estrogen receptor-negative (HR = 2.01, 95%CI: 1.41–2.86) breast cancer risk [131]. In another contemporary study, null association was observed between breast cancer risk and soy products containing isoflavones in a large cohort study of North American women although greater dairy milk intakes were associated with increased breast cancer risk, after adjusted for consumption [132]. The authors suggested that caution should be exercised when viewing existing guidelines for dairy milk intake [132].

There are meta-analyses that have indicated that higher levels of soy products and isoflavones with lower incident breast cancer risk [133, 134]. In a meta-analysis of 35 studies soy isoflavone intake has a protective effect in that it is inversely associated with breast cancer for both pre- (OR = 0.59, 95%CI: 0.48–0.69 and post-menopausal women (OR = 0.59, 95%CI: 0.44–0.74) particularly in Asian women while no evidence of a relationship in Western women [135] (**Table 3**). Nonetheless, in a previous meta-analysis of prospective cohort studies, there was no significant association between high (versus low) intake of isoflavones (RR = 0.99, 95% CI: 0.91–1.09) and moderate (versus low) intake of isoflavones (RR = 0.99, 95% CI = 0.92–1.05) and breast cancer risk, indicating that women with high dietary intake of soy isoflavones may experience decreased breast cancer incidence [136]. Support for the null finding was observed in a large Multiethnic Cohort study of women with a wide range of soya intake level and who were followed for 13 years, where no statistically association was detected between overall breast cancer risk and high dietary isoflavone intake (HR = 0.96, 95% CI: 0.85–1.08). The authors posited that higher consumption may be protective for Japanese American, Latina and African American women [137]. Notably, a recent publication of the China Kadoorie Biobank (CKB) study which involved a dose–response meta-analysis of dietary data of soy intake over a follow-up period of 10 years, the relative risk for high soy isoflavones consumption was 1.00 (95% CI: 0.81–1.22) [138]. A 3% decreased breast cancer risk for each 10 mg/day increment of soy isoflavones was observed. The results suggests that soy isoflavone was not related with breast cancer risk though increased intake may be beneficial in preventing breast cancer [138].

There are not many case–control studies that investigated the relation between soy isoflavone intake and breast cancer risk. In a case–control study conducted in Japan, increasing intake of isoflavone significantly reduced breast cancer risk in premenopausal women (OR = 0.44; 95% CI: 0.22–0.89), while no significant association was observed among postmenopausal women [139]. This shows the need to conduct more case–control studies in order to afford a clearer picture on the relationship between soy products and breast cancer incidence.

5.3 Soy proteins and soy isoflavones and breast cancer outcomes

There are studies that have examined the association between soy products and isoflavones intake and breast cancer survival, however the results are not definitive [140–142]. There are prospective cohort and meta-analyses studies that have reported significant inversely association between soy protein and soy isoflavones and breast cancer survival outcomes. In looking at prospective studies, The Shanghai Breast Cancer Survival Study comprised of 5,033 surgically treated breast cancer patients that were followed for 3.9 years. High soy protein

intake was inversely associated with breast cancer recurrence (HR = 0.68, 95%CI: 0.64–0.87) and all-cause mortality (HR = 0.71, 95%CI: 0.54–0.92) among women with either estrogen receptor-positive or -negative breast cancer [143] (**Table 2**). In an earlier prospective study of 256 Chinese women, elevated soy isoflavones intake was associated with reduced risk of breast cancer mortality (OR = 0.25, 95% CI: 0.09–0.54) and high soy protein was also concomitant with significant decreased breast cancer risk (OR = 0.38, 95% CI: 0.17–0.86) [144] (**Table 2**). In another study published in the same year involving 339 Korean women, dietary soy isoflavones was inversely related with breast cancer recurrence in HER2-positive breast cancer patients (HR = 0.23, 95%CI: 0.06–0.89) while no effect was observed with total soy intake [145].

The findings from systematic and meta-analysis of prospective cohort and case–control studies are also inconsistent. In a meta-analysis of protective studies, soy isoflavones intake was inversely linked with risk of breast cancer incidence (RR = 0.89, 95% CI: 0.79–0.99) and also inversely concomitant with risk of breast cancer recurrence (RR = 0.84, 95% CI: 0.70–0.99) [146] (**Table 3**). Likewise, Nachvak et al. conducted a systematic review and dose–response meta-analysis of 23 prospective cohort studies and reported that a 9% reduced risk of breast cancer-specific mortality for each 10 mg/day increase in soy isoflavones intake and a 12% decrease in the same survival outcome for each 5-g/day elevation of soy protein intake [147]. On the other hand, Qiu and Jiang conducted a systematic review and meta-analysis of 12 studies that explored the relationship between soy and isoflavones intake and breast cancer survival and recurrence. Pre- and post-diagnosis of soy and isoflavones intake were associated with minor reduction in risk of breast cancer recurrence (HR = 0.84 95% CI: 0.71–0.98) and breast cancer specific survival (HR = 0.89 95% CI: 0.74–1.07). Stratified analyses revealed no significant relationship between post-diagnosis soy and isoflavones consumption with overall survival (HR = 0.80, 95% CI: 0.62–1.04), and breast cancer specific survival (HR = 0.83, 95%CI: 0.64–1.07) [141].

5.4 Lycopene and breast cancer risk

The consumption of fruits and vegetables particularly those containing lycopene may offer protection against different types of cancers including breast cancer. There are a number of prospective and case–control studies that examined the relationship between dietary lycopene and breast cancer risk. In a case–control study conducted among Chinese women comprising of 122 primary breast cancer cases and 632 age-matched healthy females, high intake of dietary lycopene was statistically strongly associated with lower breast cancer risk (adjusted OR = 0.26, 95% CI: 0.14–0.46) [93] (**Table 1**). In the Women's Health Initiative Observational Study comprising 84 805 women with reported 2,879 incident breast cancer cases during a follow-up period of 7.6 years, high intake of dietary lycopene non-significantly reduced breast cancer risk by 15% (RR = 0.85; 95% CI: 0.73–1.00; P_{trend} = 0.064) in ER+ and PR+ breast cancer among post-menopausal women [23]. Also, a Swiss case–control study comprising 289 incident breast cancer cases and 442 controls reported a significant inverse association for lycopene with breast cancer risk (OR = 0.64) [148].

However, there are both prospective and case–control studies that have found null association between dietary lycopene and breast cancer risk. In a case–control study of Chinese women involving of 561 cases and 561 age-matched control high intake of lycopene was not associated with breast cancer risk (0.89, 95% CI: 0·61–1·30) [118]. Likewise, in another case–control study of non-Hispanic White and Hispanic women there was no association and therefore no protective effect of

dietary lycopene on breast cancer risk [60]. Furthermore, there are other studies of dietary lycopene intake including prospective cohort [57, 88, 105, 146], case–control [149] and meta-analysis [91] that have found no association of lycopene with breast cancer risk.

Epidemiologic studies evaluating whether circulating lycopene is associated with breast cancer risk have yielded equivocal answers. A nested case–control study conducted comprising 295 breast cancer cases and 295 age- and race-matched controls demonstrated significantly strong inverse association of high levels of lycopene with the risk of developing breast cancer [97]. In another case–control study among women in the United States (46 breast cancer cases and 63 controls), there was a strong inverse association of lycopene (OR = 0.32, 95% CI: 0.11 -, 0.94) in breast adipose tissue and risk of breast cancer [150] (**Table 1**). Likewise, a pilot case–control study of Caucasian and African American women found a weak inverse relation between plasma lycopene concentration and risk of breast cancer (Simon et al., 2000). The findings of these study were in agreement with that of a comprehensive pooled analysis of 8 prospective cohort studies conducted by Eliassen and colleagues. They found serum or plasma levels of lycopene significantly lower the risk of breast cancer patients by 22% (RR = 0.78, 95% CI: 0.62–0.99, P_{trend} = 0.02) [151] (**Table 3**).

Others studies with findings in consonant with an inverse association between serum or plasma levels of lycopene and breast cancer risk include two case–control studies that showed deceased risk among females with elevated mammographic density [152] and blood donors [103] and a nested case–case control in the Nurses' Health Study [153]. Likewise, in a nested case–control study, stepwise increase in plasma lycopene levels were not associated (RR = 0.95, 1.15, 0.93, 1.00 (reference, P trend = 0.86) with decreased breast cancer risk in older and middle-aged females [154].

5.5 Lutein and zeaxanthin and breast cancer risk

There are a few epidemiologic studies that have investigate the protective effect of dietary lutein and zeaxanthin on breast cancer incidence [90, 119, 155]. A case–control study of Chinese women found that lutein/zeaxanthin reduced breast cancer risk by 51% (OR = 0·49, 95% CI: 0·34–0·71) particularly among premenopausal women and those exposed to second-hand smoke [119]. In an earlier large population-based case–control study of United States residents, an inverse association was shown for higher consumption of lutein/zeaxanthin (OR = 0.83, 95% CI 0.68–0.99, P_{trend} = 0.02) and breast cancer risk among postmenopausal women [90]. Likewise, Bae conducted a pooled analysis of eighteen prospective cohort studies and reported that lutein/zeaxanthin demonstrated protective effect on ER- and PR+ as well as ER-/PR- breast cancer [155].

However, a case–control study of Chinese women demonstrated that high dietary lutein/zeaxanthin were not inversely associated with breast cancer risk [93]. Similarly, in a large cohort study of Canadian women Terry et al. reported no clear association between dietary intake of lutein/zeaxanthin and risk of breast cancer [88]. In a later meta-analysis involving 33 studies, high dietary intake of lutein/+zeaxanthin offered no protective effect and thus no significant association with breast cancer risk [91].

In addition to epidemiological studies that have discovered the anti-cancer potential of dietary lutein/zeaxanthin, there are a few research that investigated the protective role of this circulating antioxidant. Serum or plasma levels of lutein/zeaxanthin are more suitable biological indicators of the amount of these flavonol available for chemo-preventative action [156]. In a case–control study conducted

among Chinese women, there was a significantly strong inverse association of high serum levels of lutein/zeaxanthin with breast cancer risk (OR = 0·26, 95% CI: 0·17–0·38) [157]. Likewise, a nested case–control study comprising 604 incident breast cancer cases and 626 controls in the Nurses' Health Study found that circulating lycopene, alpha-carotene and beta-cryptoxanthin were concomitant with a significant 40% - 50% decrease in the risk of breast cancer ($P_{trend} < 0.05$) [152]. These findings were corroborated by a comprehensive analysis of 8 cohort studies where lutein/zeaxanthin was significantly inversely associated with breast cancer risk (RR = 0.84, 95% CI: 0.70–1.01, $P_{trend} = 0.05$) [151]. Interestingly, in a nested case–control study (270 breast cancer cases, 270 matched controls) the risk of breast cancer increased due to low blood levels (OR = 2.08, 95% CI: 1.11–3.90) [158].

However, In a nested case–control study (1502 breast cancer cases and 1502 individually matched controls) conducted within the European Prospective Investigation into Cancer and Nutrition cohort, there was no statistical association of plasma levels of lutein with of ER- breast tumors [98]. Supporting evidence was also observed in a case–control cohort (201 breast cancer cases and 290 referents) where plasma concentrations of lutein was significantly inversely related with breast cancer risk in premenopausal women [106].

5.6 Quercetin and breast cancer risk

The number of epidemiological research involving quercetin and potential relationship with breast cancer risk is lacking. In a linkage of multi-centered case–control studies conducted in Italy (comprising 10,000 incident breast cancer cases and 16,000 controls) high intake of flavonols including quercetin was inversely associated with breast cancer risk (OR = 0.80) [158]. Similarly, in an earlier large-case control study also conducted in Italy (2,569 incident breast cancer cases and 2,588 controls), increasing consumption of flavonols decreased breast cancer risk by 20% (OR = 0.80; $_{Ptrend,}$ 0.06) [111]. The findings of another large case–control study comprising Greek women was consistent with these two previous results where a strong significant inverse relationship of daily flavonols in fruit comprising quercetin with breast cancer risk [114]. Higher intake of quercetin reduced breast cancer risk by 38% (RR = 0.62, 95%CI: 0.37–1.03, P = 0.25) and the relation was stronger when modification was made in lieu of other dietary sources with a lower risk of 46% (RR = 0.54, 95%CI: 0.30–0.95, P = 0.14) [120]. Lastly, in a meta-analyses of 6 case–controls and 6 prospective cohort studies, breast cancer risk due to high intake (compared with low consumption) of flavonols such as quercetin declined by 12% in females (RR = 0.88, 95% CI: 0.80–0.98). It was also observed that further analyses of 3 case–control studies, high flavonol intake (compared with low consumption) was associated with decreased breast cancer risk in post-menopausal women [116].

6. Green tea

6.1 Green tea intake and breast cancer risk

Green tea is a product of dry tea leaves of the plant *Camellia sinensis*, and numerous pre-clinical and epidemiologic studies have been conducted examining the possible protective effect of green tea from various types of human cancers including breast carcinoma [159]. Epidemiologic studies have described a protecting effect of green tea consumption against the initiation and progression of breast cancer, although the results has not being conclusive. A case–control study (1009 incident

breast cancer cases and 1009 age-matched controls) of regular green tea (dried green tea leaves per annum) consumption in a dose-dependent manner significantly reduced breast cancer risk [(OR = 0.87, 95% CI: 0.73–1.04) for 1–249 g; (OR = 0.68, 95% CI: 0.54–0.86) for 250–499 g and (OR = 0.59, 95 CI: 0.45–0.77) for 500–749 g, $P_{trend} < 0.001$) [160]. Likewise, in a population-based, case–control study of Asian women with breast cancer (501 breast cancer patients and 594 controls), there was a significant trend of reducing risk with cumulative amount of green tea consumption ([OR = 0.71, 95% CI: 0.51–0.99) and (OR = 0.53, 95% CI: 0.35–0.78) for 0–85.7 ml and > 85.7 ml of green tea per day respectively] [161]. These findings were corroborated by a population-based case–control study of Chinese women in which regular green tea mildly decreased breast cancer risk by 18% (OR = 0.88; 95% CI: 0.79–0.98). It was observed that a dose-dependent association existed with the quantity of green tea intake per month and catechol-O-methyltransferase rs4680 genotypes did not modify the relationship [162].

Two other nested case–control studies are consistent with the protective effect of green tea consumption. Yuan et al. piloted a nested case–control study (297 incident breast cancer cases and 665 controls) inside the Singapore Chinese Health Study and found that frequent green tea consumption significantly decreases breast cancer risk in women with high angiotensin-converting enzyme activity (OR = 0.33, 95%CI: 0.13–0.82, $P_{trend} = 0.039$) [163]. In an earlier nested case–control study (380 incident breast cancer cases and 662 controls) also within the Singapore Chinese Health Study, women with low folate intake and daily or weekly green tea consumption had a 55% reduced breast cancer risk (OR = 0.45, 95% CI: 0.26–0.79, $P_{interaction} = 0.02$). Green tea consumption was not associated with breast cancer risk at high folate intake and the authors suggested that inhibition of the folate intake may be a possible mechanism which account for the protective effect of green tea against breast carcinoma [164].

There are two meta-analyses that support the reduction of breast cancer incidence and recurrence due to green tea consumption. A meta-analysis of studies by Ogunleye et al. of breast cancer recurrence and risk comprising 5,617 cases showed that increased green tea intake (greater than 3 cups/day) was inversely related with breast cancer recurrence ($RR_{pooled} = 0.73$, 95%CI: 0.56–0.96 [165] (Ogunleye et al., 2010). An analysis of only case–control studies showed that the inverse relationship was preserved ($RR_{pooled} = 0.81$, 95%CI: 0.75–0.88) while there was no protective effect and therefore null association of breast cancer risk among prospective cohort studies [165]. There was additional supportive evidence in a more recent meta-analysis of 13 studies (5 case–control and 8 cohort studies comprising of 63,810 women) where a statistically significant inverse association existed between green tea consumption and breast cancer incidence with a 15% risk reduction ($OR_{pooled} = 0.85$, 95% CI: 0.80–0.92, p = 0.0001) [166]. Analysis of only case–control studies also showed a significant inverse relationship with a 19% decrease in the risk of breast cancer (ORpooled = 0.81, 95%CI: 0.74–0.88, p = 0.000) [166].

The results of prospective cohort studies demonstrating a protective effects against breast cancer were less conclusive with some of the studies reporting null association. In a prospective cohort study of the Hospital-based Epidemiologic Research Program in Japan, there was reduced breast cancer recurrence among subjects who consumed 3 or more cups of green tea (HR = 0.69, 95%CI: 0.47–1.00), particularly in stage I disease (HR = 0.43, 95%CI: 0.22–0.84) [167]. In the Shanghai Women's Health Study, a large population based study comprising 74,942 Chinese females, subjects who began drinking green tea less than or at 25 years of age were less likely to develop breast cancer (HR = 0.69, 95% CI: 0.41–1.17) [168]. However, in a later population-based prospective cohort study also conducted in Japan, there was no association of breast cancer risk and green tea consumption (> 5 or more

cups/day; HR = 1.12, 95%CI: 0.81–1.56; P_{trend} = 0.60) [169]. Green tea intake was not associated with a reduced breast cancer risk in another prospective study conducted in Japan [170] and in 2 prospective studies piloted among 35,004 Japanese women (RR = 0.84, 95%CI: 0.57–1.24; > 5 cups/day) [171].

6.1.1 Epigallocatechin-3-gallate intake and breast cancer risk

Epigallocatechin-3-gallate is a natural antioxidant and it has been reported to be more efficient at arresting reactive oxygen species and other radical than vitamin C and E [172]. Experimental studies have demonstrated that epigallocatechin-3-gallate, the biologically active and most abundant tea catechins displays anticancer and chemotherapeutic effects against breast cancer [173]. Epidemiologic studies relating to epigallocatechin-3-gallate are lacking. In a nested case–control study (144 incident breast cancer cases and 288 age-matched controls) in the Japan Public Health Center-based Prospective Study, elevated plasma levels of epigallocatechin-3-gallate along with epicatechin-3-gallate, epicatechin and epigallocatechin were not associated with reduced breast cancer risk [epigallocatechin-3-gallate (OR = 1.21, 95%CI: 0.52–2.80; P_{trend} = 0.53)] [169]. In another study published three years ago, green tea extract capsules comprising 843 mg epigallocatechin-3-gallate administered for 1 year decreased mammographic density in healthy postmenopausal women [174]. Interesting, epigallocatechin-3-gallate (400 mg capsules, 3 times/day for 2–8 weeks) orally administered to breast cancer subjects undergoing radiotherapy potentiate the effectiveness of the treatment as evident by decreased metalloproteinase-9 and metalloproteinase-2 activities and elevated serum concentration of vascular endothelial growth factor [175].

The few reports of epidemiologic evidence of epigallocatechin-3-gallate and inconclusive findings in prospective studies suggests that further exploration of its probable chemo-preventative.

7. Discussion and conclusion

The epidemiological evidence shown by a number of case–control, prospective cohort studies as well as meta-analysis and systematic reviews presented does support the view that nutritional micronutrients with antioxidant properties in dietary or supplemental form may be beneficial in protecting women against breast cancer. However, there are studies that have demonstrated null association between the dietary and supplemental micronutrients, and the risk or survival outcomes of breast cancer. Thus overall the findings are inconsistent and epidemiological data on some of the antioxidants as it relates to breast cancer outcomes such as recurrence, and breast cancer-specific and all-cause mortality is inadequate.

Notably, there is substantial evidence which is well documented in the literature of the protective action and modification of many signaling pathways and molecular events by these antioxidants inducing apoptosis, inhibition of breast cancer cell proliferation and invasion, and preventing angiogenesis and metastasis. However, the findings of epidemiological results are somewhat disappointing and are not concurrent with experimental results for most of these natural antioxidants. There are limiting factors which negatively impact epidemiological association studies such as genetic, confounding lifestyle, samples sizes, possible selection bias in case–control studies, the length of intervention, possible recall bias in retrospective studies, not accurately measuring dietary intake in prospective studies, interaction among different micronutrients which may nullify individual effect among others.

Nevertheless, despite the inconsistencies, the findings of the chemo-preventative effects of vitamins, flavonoids and green tea presented in this review are encouraging. There need to be more large-scale and randomized controlled studies to investigate the association of these antioxidants and outcomes such as breast cancer recurrence, and breast cancer-specific mortality. More studies investigating the dietary intake of these antioxidants with sub-types of breast cancer, namely ER and PR status among both premenopausal and postmenopausal women is warranted. The elucidation of the mechanism of action by which these antioxidants decrease breast cancer risk may be helpful in recognizing sub-groups who could benefit from the consumption of these antioxidants with better dietary endorsements for the prevention of breast cancer.

Furthermore, the finding that the inhibition of folate intake may be a possible mechanism which account for the protective effect of green tea against breast cancer is noted. Large prospective randomized control trials are warranted as they could provide definitive information on the beneficial or harmful effects of green tea intake on breast cancer development.

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