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Vitamins, Carotenoids and its association with Beneficial Effect in Preventing Breast Cancer

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Abstract — **Breast cancer is the second most common cancer in women. Vitamins have been highlighted in numerous studies for its antioxidant properties and its influence on cell physiology, which suggest its potential on tumor prevention. This review aims to verify the effects of intake and/or supplementation of vitamins A, C, D and E in breast cancer prevention. The search was performed in PubMed. For this review, a search was performed using several pre-defined keyword combinations and their equivalents: "Vitamin A", "Carotenoids", "Ascorbic Acid", "Vitamin E", "Tocopherols", "Vitamin D". It was included Clinical Trials, Randomized Controlled Trials, Reviews and Systematic Reviews between January 2002 and December 2014, with women older than 18 years. Initially, 85 studies were identified. However, only twenty five were eligible. It has been demonstrated that vitamin D can reduce the risk of breast cancer in women, as well as vitamin E. Carotenoids and vitamin C might provide beneficial effects in subgroups like premenopausal and postmenopausal women respectively, being influenced by the menopausal status.**

Index Terms— **breast cancer, vitamins, prevention**

I.INTRODUCTION

In the last century, an epidemiological transition occurred, leading to a reduction of the infectious diseases prevalence, and an increase of chronic diseases incidence, especially neoplasms. Besides, the growth in life expectancy and the aging of population over the past decades have also contributed to enhance the incidence of these diseases [1].

Breast cancer is one of the most frequent cancer in women. In 2014, it was expected 57.120 new diagnosed cases in Brazil [2]. This disease still represents a serious public health problem throughout the world, because of the high morbidity and mortality and high cost of the treatment [3]. In Brazil, data from the Ministry of Health indicate breast cancer as responsible for 12.705 deaths in women in 2010 [4] and for almost 4.000 hospitalizations in 2012 [5].

Several factors influence the onset and development of cancer. Thus, it can be cited as internal causes, the genetic susceptibility of individuals and their own aging process. Furthermore, external causes as lifestyle and dietary habits are importantly included [2].

Nowadays, health policies are focused on early detection of breast cancer, secondary prevention, by mammography screening in women over 40 years old [2]. Primary prevention strategies should be encouraged. Vitamins have been highlighted in numerous studies for its antioxidant properties and its influence on cell physiology, purposing its potential anticarcinogenic role and tumor prevention [6-9].

Vitamin A and retinoids are substances with diverse biological actions. They are essential on cell growth, differentiation and proliferation, besides embryogenesis and apoptosis. These compounds have promoted beneficial effects in tumor cells *in vitro* and *in vivo* [10] . Breast cancer tumors show suppression of nuclear retinoic acid receptors, which are believed to be involved in the carcinogenesis process [10, 11] .

Metanalysis of carotenoids and breast cancer, evaluating papers between 1982 and 2011, demonstrated that α-carotene intake may reduce the risk of breast cancer. However, the association of β-carotene with breast cancer remains to be investigated. This association still cannot be established for β-cryptoxanthin, lutein/zeaxanthin and lycopene [12] .

Vitamin C has antioxidant properties and also works as enzyme cofactor in plants and animals. It is not synthesized by humans and then must be obtained from diet. Ascorbic acid is the predominant form in humans. This is a powerful antioxidant that neutralizes efficiently free radicals produced in potentially harmful biological processes. Nevertheless, at higher concentrations has pro-oxidant action, leading to degradation of molecules and cell structures. This effect is greater in tumor cells, due to lower concentration of antioxidant enzymes in the cell. Moreover, in the presence of transition metals, such as iron, copper, cobalt, manganese,

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chromium and with increased ascorbic acid oxidation, the cytotoxic effect on tumor cells is enhanced [13, 14, 11] .

Vitamin D is obtained by skin exposure to ultraviolet rays or from the diet. It is soluble in lipids and essential on immune system and bone development. It exhibits a protective effect against the tumor cells proliferation, since it is involved in calcium and phosphorus levels. The 1,25-dihydroxyvitamin D stimulates macrophages in many genes responsible for cell proliferation, apoptosis, angiogenesis and cell differentiation [15, 16] . Mortality in some type of cancers is inversely proportional to the level of sun exposure. In addition, the supplementation of vitamin D can be able to diminish cell proliferation of prostate and bowel cancer [17, 18, 11, 19].

Vitamin E, also fat-soluble, is an essential component of cell membranes, regulating gene expression, signaling, and cell proliferation. Tocopherols (α-, β-, γ-, δ-) and tocotrienols (α-, β-, γ-, δ-) are the chemical forms of vitamin E. The α-tocopherol is the most abundant form in human tissues and has also antioxidant and anti-inflammatory properties [20] . Its potential regulatory mechanism on cell proliferation and differentiation, through inhibition of protein kinase C, can inhibit tumor development [11, 21] .

Thus, the present review aims to verify the effects of intake and/or supplementation of carotenoids and vitamins A, C, D and E in the prevention of breast cancer.

II. MATERIALS AND METHODS

The search was conducted in PubMed from 2002 to 2014, using the following descriptors: "Vitamin A", "Carotenoids", "Ascorbic Acid", "Vitamin E", "Tocopherols", "Vitamin D", "prevention and control", "Breast Neoplasms", "Humans", "Women", "Female", "Adult".

The types of studies "Article Types", "Clinical Trial", "Randomized Controlled Trial", "Review", "Systematic Reviews", and studies with human female and over the age of 19 years were considered as limits. Firstly, the database identified 85 studies. Titles and abstracts were checked and 43 studies were excluded. Then, after full text reading, papers were selected according to the following inclusion criteria: studies with vitamin A or carotenoids, vitamin C, D and E or tocopherol, alone or together, in the prevention of primary breast cancer in adult women. There were restrictions regarding the language, accepting only those papers published in English, and to the time of publication, in the last 12 years. Animal studies were excluded. All papers were analyzed carefully by two researchers, and in case of disagreement, a third investigator was consulted.

The methodological quality of the selected papers was evaluated according to the PEDro scale, based on the Delphi list. Studies with PEDro score less than 3 were considered to have low quality and were excluded [22] .

From the selected papers, 13 covered the relationship between cancer and vitamin D. In addition, eight of them, strictly involved this vitamin [23-28, 8, 29] and five of them also included calcium [30-34] . One of them evaluated calcium and a subanalysis with vitamin D [33]. Another one reported the effect of vitamin D on estrogen and progesterone levels and the possible benefits on breast cancer [27]. Regarding the vitamin A, six studies encompassed only carotenoids [35-37, 6, 38-40] . Other studies evaluated vitamin A or carotenoids combined with vitamin E [35] and tocopherol [41] and multivitamins [42] . The vitamin E in combination with fruit and vegetables intake was assessed in one paper [43]. A study regarding vitamin C alone and breast cancer [44], and a cohort study that evaluated vitamin C, vitamin E and β-carotene and breast cancer risk [45] were also found.

This review included 4 types of studies, seven of them were cohort studies [24, 36, 41, 37, 33, 34, 45], fourteen were case - control [30, 35, 32, 23, 42, 44, 46, 28, 43, 6, 8, 38, 39, 29], three were intervention [31, 32, 27], two were a meta-analysis [36, 40], one was a pooled analysis of eight cohort studies [36] and one a pooled analysis of eighteen cohort studies [40].

III. RESULTS AND DISCUSSION

Twenty five papers were carefully selected for this review. Most of the studies included vitamin D (13 papers) with or without the presence of calcium. The others evaluated carotenoids, vitamin C and vitamin E, alone or in combination.

A meta-analysis of 18 cohort studies, involving carotenoids and the risk of developing breast cancer, evaluated almost 1.1 million women, according to the status of estrogen (ER) and progesterone receptor (PR). Some of them were followed up during 26 years. Interestingly, they found an inverse association between carotenoids intake (α-carotene, β-carotene and lutein/zeaxanthin) and ER negative breast cancer. However, no relationship with breast cancer was observed in those ER positive [40].

A study assessing carotenoids (α- and β-carotene, β-cryptoxanthin and lutein/zeaxanthin) intake among Chinese women case-control study, found an inverse association between consumption of carotenoids and risk of breast cancer, except for lycopene. The benefits were even greater among pre-menopausal women and second-hand smoke women, and also was observed for all subtypes of breast cancer' hormone receptor status. [39].

A pooled analysis of eight cohort studies, with 3956 cases and 3055 controls, found that women with higher circulating levels of α-carotene, β-carotene, lutein+zeaxanthin, lycopene, and total carotenoids may have reduced risk of breast cancer, with more benefit for women with estrogen-receptor-negative breast cancer. No protective benefit was found for β-cryptoxanthin [36].

Another study assessing carotenoids (α- and β-carotene) intake in a Swedish women cohort, with a mean time of 9.4 years found an inverse association between consumption of carotenoids and risk of ER negative breast cancer in smokers and in those not taking dietary supplements [37].

A case-control study involving women with breast cancer found inverse association between vitamin A, β-carotene, lutein/zeaxanthin high consumption levels and the risk of breast cancer in premenopausal women, with better outcomes in smokers' women. Among those postmenopausal, this benefit was not demonstrated [6].

The relationship between lycopene intake, its serum levels and the risk of developing breast cancer was also studied in a cohort and in a case-control subgroup analysis. The cohort study categorized the women into quintiles of dietary lycopene and followed them for about nine years. The case-control study was performed with 508 breast cancer cases and 508 controls No source of lycopene was related to breast cancer, and no correlation was observed between lycopene intake, its serum levels and the risk of developing breast cancer [38] .

Carotenoids (α-carotene, β-carotene, β-cryptoxanthin, lycopene, lutein/zeaxanthin), retinol and tocopherols (α- and γ-tocopherol) plasmatic levels were measured in postmenopausal women. The mean follow-up was 8 years. A positive association was found between baseline levels of γ-tocopherol, lycopene and the risk of developing breast cancer. On the other hand, reduced risk of breast cancer was verified with the baseline level of α-carotene and the serum concentration of α and β-carotene one and three years before diagnosis [41].

Regarding the self-reported vitamin supplementation use (multivitamin, A, B, C, and E) in women with breast cancer, who participated of The Shanghai Breast Cancer Study, a case-control study conducted in two phases (1996-1998 and 2002-2004), showed that the risk of breast cancer disease was not related to the consumption of vitamins A, B, C and E. However, in those with low vitamin E intake, supplementation may reduce this risk in 20% [42].

In a Chinese women cohort study performed by Malin et al (2003), fruits and micronutrients intake were evaluated, including the association of vitamin E and breast cancer. The results suggested that the risk of developing breast cancer could be inversely related to the vitamin E consumption, but the intake of total carotene, vitamin C, retinol and total vitamin A was not related with breast cancer risk [43].

In a case-control study with Mexican women, reduced risk of breast cancer was associated with high carotenoids intake in premenopausal women and also with high vitamin E and polyunsaturated fat intake in postmenopausal ones [35].

A nested case–control study with dietary vitamin C intake, estimated from 4-7 day food diaries, was performed with women who participate from five prospective studies in the UK Dietary Cohort Consortium. In this study no evidence of associations between breast cancer incidence and dietary or total vitamin C intake was found, even in post-menopausal women sub-analysis [44].

A prospective cohort study that evaluated vitamin C, vitamin E and β-carotene at the same time, also found no evidence for an overall association between intake of β-carotene, vitamin C and E and breast cancer risk in pre- and postmenopausal women. However, an inverse association between dietary β-carotene and breast cancer for women consuming moderate to high amounts of alcohol was observed. Results of subgroup analysis suggested a protective effect of the intake of vitamin C and high intake of β-carotene in some subgroups of postmenopausal women, notably those using exogenous hormones [45].

Li, J.et al [33], in a prospective cohort study, found no association between calcium intake and breast cancer risk, using an in-person interviewer and a validated food frequency questionnaire, even in women with dietary vitamin D below or above median, 83.2UI/day .

A case-control study with Saudi Arabian women found low dietary vitamin D intake in breast cancer cases and control. The serum concentration of 25(OH)D was lower in cases than in controls, with an inverse association between 25(OH)D serum concentrations and breast cancer risk [29]. Lee, M.-S.et al [28], in a study with Taiwan women, found a protective effect of vitamin D intake and breast cancer risk in premenopausal women, especially in those with Body Mass Index (BMI) less than 24 kg/m^2, independent of sunlight exposure.

In a 10- years follow-up study of a French cohort, with about 67.721 women included, no association was found between dietary and supplemental vitamin D intakes and breast cancer risk. Among post-menopausal women from regions with the highest daily ultraviolet radiation doses, those with high dietary or supplemental vitamin D and high UV exposure had benefit in the reduction of breast cancer risk. Vitamin D obtained from sun exposure and from dietary sources can provide benefits related to the risk of breast cancer, suggesting that in areas of low dietary intake and/or sun exposure, dietary supplementation should be encouraged [25].

The evaluation of the vitamin D influence on female fertility and on sex hormone levels in 101 young women was performed by Knight, J. A.et al [27]. Vitamin D supplementation was associated with reduced levels of estrogen and progesterone. This correlation, in a long-term, could be related to a decreased risk of developing breast cancer. Serum levels of vitamin D have also been used to predict this risk. According to Crew, K.et al [23] women that had vitamin D doses above 40 ng/mL had decreased risk of breast cancer, with greater reduction in postmenopausal women, when compared to those women with deficiency of this vitamin (<20 ng/mL).

Rossi, M.et al [8] also found an inverse association between vitamin D intake and the risk of developing breast cancer, regardless of menopausal status. It has also been observed that differences in eating habits related to vitamin D may be partly related to this effect.

When vitamin D obtained from the diet or from sun exposure was evaluated at different stages of life, the protective effect was found in those women who had a history of sun exposure mainly between 10 and 19 years old, period of breast development. Similarly, it was also demonstrated an inverse correlation between the amount of milk intake in

adolescence and young adulthood and the risk of developing breast cancer. This benefit was lower in those women whose exposure to vitamin D occurred mainly between 20 and 29 years old. No benefit was found in women over 45 years old [26].

Edvardsen, K.et al [24] evaluated vitamin D intake, sun exposure, including history of UV-exposure, information on sun-seeking holidays, use of solarium and frequency of sunburn, and the risk of breast cancer and did not found association of these factors with breast cancer risk. In addition, Chlebowski, R.et al [32] observed that dietary supplementation of calcium and vitamin D also did not decrease the incidence of invasive breast cancer in postmenopausal women. Furthermore, serum levels of 25-hydroxyvitamin D were not related to the breast cancer risk.

In a study including almost 37.000 postmenopausal women from the Women's Health Initiative (WHI), the association of calcium and vitamin D intake with breast cancer was evaluated. The results showed that the risk of breast cancer progression was reduced by 14-20%, in women who were supplemented with vitamin D without a personal supplements use [31].

Abbas, S.et al [30] evaluated the effect of vitamin D and calcium from the diet in premenopausal women. Only vitamin D intake showed a protective effect in breast cancer risk. No correlation between calcium intake or its combination with vitamin D was observed. In another study [34], an inverse effect of both vitamin D and calcium total intake with the risk of developing breast cancer in premenopausal women, but not in postmenopausal women was noted.

The relationship between vitamin D and breast cancer was evaluated by the different types of study. From four cohorts, with a total of 175.047 women evaluated, two of them (with a total of 99.208 women) found benefit. Six case-control studies were included, and five of them found a protective effect of vitamin D. Concerning the interventional studies, reduced risk of breast cancer with vitamin D and calcium supplementation was observed in a study by Bolland, M.et al [31]. Nevertheless, in those who were already supplementing by their own, when they received extra calcium or vitamin D supplementation the benefit was not found. In 2007, the first analysis of these patients showed no relationship between dietary supplementation vitamin D and calcium and breast cancer risk. Moreover, in a case-control subanalysis, no correlation was found between the 25-hydroxyvitamin D serum levels before the supplementation(baseline levels breast cancer cases 50.0 ±21.0 nmol/L and controls 52.0± 21.1 nmol/L) and risk of breast cancer [32].

Despite the above mentioned studies and extensive discussion in the scientific literature, we believe that still there is not a consensus on the recommendations of vitamins and carotenoids. Therefore, further clarification regarding the beneficial effect of these compounds in the human metabolism and prevention of breast cancer is needed. The vitamin D supplementation seems to be protective in relation to breast cancer, even without a consensus on the role of dietary source or supplement on this benefit. The effect of vitamin D on breast cancer risk also seems to be different according to the menopausal status of women.

IV. CONCLUSION

Vitamins, with its antioxidant properties, have potential antitumor action which can be more explored in cancer prevention. Vitamin D, associated or not with calcium, has been demonstrated to reduce the risk of breast cancer in women. However, more studies are needed to define the role of the sun exposure in the prevention of this type of tumor and the extension of the benefit according to the menopausal status.

The vitamin C can have a protective effect in some subgroups of postmenopausal women. Concerning carotenoids and vitamin E, the effect on breast cancer is still not clear. It seems that carotenoids might provide beneficial effects in premenopausal women, although the same does not occur in postmenopausal ones, while vitamin E may reduce the risk of breast cancer in both pre and postmenopausal.

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Table I: Summarizes studies relating breast cancer and vitamins A, C, D and E.

Author, year, country and type of study	Estimated nutrient	Target Population	Observed effect	Supplementation	Method	Follow-up/ Recruit
Wang *et al*, 2014, China, hospital-based case-control	Carotenoids	1.122 women	Inverse association with breast cancer risk and the highest vs lowest quartile of intake of α-carotene (<326·37vs>945·61, OR 0.61, 95% CI 0·43,0·88), β-carotene (<3933.00 vs >. 8382.49, OR 0.54, (95% CI 0.38, 0.78), β -cryptoxanthin (, <49.76 vs >135.17, OR 0.38 (95% CI 0.26,0·52) and lutein/zeaxanthin (<3510·94 vs > . 7999·28, OR 0.49, 95% CI 0.34, 0.71).	There was no supplementation	Food Frequency Questionnaire (FFQ)	Ongoing, beginning in September 2011
Li, *et al,* 2013, China, cohort	Calcium and vitamin D	34.028 women	No association between Calcium and breast cancer risk (highest quartile >345.6 mg/1000 kcal/day compared to lowest quartile <204.5mg/1000 kcal/day of intake	There was no supplementation	Food Frequency Questionnaire (FFQ)	Follow-up mean 14.2±3.5 years
Yousef, *et al,* 2013, Saudi Arabia, case-control	Vitamin D	240 women	Inverse association. Women with 25(OH)D ≥10 and <20ng/mL- OR 4.0 (1.6-10.4 95% CI). Women with 25(OH)D <10ng/mL OR 6.1 (2.4, 15.1CI) for breast cancer risk compared to those with 25(OH)D concentrations >20ng/mL	There was no supplementation	Food-frequency questionnaire (FFQ) Serum samples	June to August 2009
Eliessen *et al*., 2012, USA, pooled analysis 8 cohort studies	Carotenoids	10.066 women	Inverse association with breast cancer. High vs lowest quintile for α-carotene(<2.6vs ≥11.3, RR 0.87, 95% CI = 0.71, 1.05, Ptrend = 0 .04), β-carotene (<11.9 vs ≥39.9, RR 0.83, 95% CI 0.70, 0.98), lutein+zeaxanthin (<16.9 vs ≥37.3, RR 0.84, 95% CI 0.70, 1.01, Ptrend 0.05), lycopene (<15.7 vs ≥45, RR 0.78, 95% CI 0.62, 0.99), and total carotenoids (<70.1 vs ≥139, RR 0.81, 95% CI 0.68,0.96)	There were women with and without supplementation	Plasma or serum samples collected	_
Hutchinson *et al*, 2012, UK, nested case control	Vitamin C	2.851	No association	There were women with and without supplementation. Mean dietary vitamin C intake: 66 to 118 mg/day. Mean total vitamin C intake: 118 to 251 mg/day	Food Frequency Questionnaire (FFQ)	_
Zhang *et al*., 2012, USA, meta-analysis pooled analysis 18 cohort	Carotenoids	1.028.438 women	Carotenoids intake inversely associated to ER negative breast cancer (highest vs lowest quintiles: α-carotene RR 0.87; 95% CI: 0.78, 0.97), β-carotene RR 0.84; 95% CI: 0.77, 0.93), and lutein/zeaxanthin RR 0.87; 95% CI: 0.79, 0.95)	There was no supplementation	Food Frequency Questionnaire (FFQ)	_
Bolland *et al*., 2011, New Zealand, intervention/clinical trial	Vitamin D and calcium	36.282 postmenopausal women	Reduces risk of breast cancer	1 g Ca 400 IU vitamin D daily	Food Frequency Questionnaire (FFQ) And supplement use questionary	7 years
Lee *et al*., 2011, China, case-control	Vitamin D	400 women	Protective effect (lower breast cancer risk in women with a dietary vitaminD intake > 5 µg/day (OR 0.48; 95% CI, 0.24–0.97) than women with an intake < 2 µg/day	Vitamin D supplement 3.48µg± 5.10 cases and 3.64µg ±5.02 µg/day control. 47.5% cases and 55.5% control	Food Frequency Questionnaire (FFQ)	Recruitment 2004–2005
Engel *et al*., 2011, France, cohort	Vitamin D	67.721 women	No association between dietary and supplemental vitamin D intakes and breast cancer risk. Protective effect in highest quartile daily ultraviolet radiation dose region(>2.7 kJ/m^{2}d in postmenopausal women with high tercil(>113IU/d, mean 143.2 IU/d)) dietary or supplemental vitamin D intake compared to lowest	There were women with and without supplementation	Food Frequency Questionnaire (FFQ)	follow-up 10 years
Edvardsen *et al*., 2011, Norway, cohort	Vitamin D	41.811 women	No effect	There was no supplementation. Mean vitamin D baseline intake : 9.4 µg/day	Food Frequency Questionnaire (FFQ)	Follow-up 8.5 years
Nagel *et al*., 2010, Europe, Cohort	Beta-carotene, vitamin C and vitamin E	288.776 women	In postmenopausal women with hormone replacement and alcohol consumption, a weak protective effect between b-carotene (highest 28,742 mg/d vs. lowest 22,606 mg/d quintile) and vitamin E (highest 28,742 mg/d vs. lowest 22,606 mg/d quintile)	There were women with and without supplementation.Median intake (mg/day): β-Carotene: 1.6 to 4.05. Vitamin C: 95.88 to 200.82.Vitamin E: 7.28 to 13.33	Country-specific validated questionnaires to capture local dietary habits(face-to-face dietary interview, quantitative, semi quantitative, dietary questionnaire combined with food records)	median follow-up time of 8.8 years
Larsson *et al*., 2010, Sweden, cohort	Carotenoids	36.664 women	α and β-carotene inversely associated with the risk of breast cancer among smokers (highest ≥ 1650 µg/d vs lowest <318 µg/d quintile of intake- 0.32 (95% CI 0.11–0.94; Ptrend = 0.01) for α-carotene and highest ≥4783 µg/d vs lowest <1774 µg/d quintile 0.35 (95% CI: 0.12–0.99; Ptrend = 0.03 for β-carotene) and in women who do not use dietary supplementation	There was no supplementation	Food Frequency Questionnaire (FFQ)	Recruitments 1987 to 1990, and 1997. Follow up 1998 to the date of breast cancer diagnosis, death, or December 31, 2007

Knight *et al.*, 2010, intervention	Vitamin D	101 women	Potential reduction	Vitamin D = 4 weekly doses of 28,000 IU(D_3)	Blood sample	Recruitment in summer (June to September) and in winter (December to March)
Kabat *et al.*, 2009, EUA, cohort	Carotenoids/ retinol/ tocopherol	5.450 women	Inverse association between the baseline serum α-carotene and the β-carotene and breast cancer. γ-tocopherol and lycopene – direct associacion (highest compared with lowest tertile)	No supplementation	blood samples years 1, 3 and 6 follow-up	Recruit 1 October 1993 and 31 December1998 Median follow-up 8 years
Crew *et al.*, 2009, EUA, population-based case-control	Vitamin D	2101 women	Protective effect, greater in postmenopausal women	-	Food Frequency Questionnaire (FFQ) Plasma	Cases recruitment between August 1, 1996, and July 31, 1997
Mignone *et al*, 2009, EUA, case-control	Carotenoids	12268 women	In Premenopausal women, an inverse association with breast cancer was observed for high levels of vitamin A(>2309.6) (OR: 0.82, 95%CI: 0.68–0.98, p for trend = 0.01), β-carotene (>25022.9 mcg) (OR: 0.81, 95% CI 0.68–0.98, ptrend = 0.009), α-carotene (> 5686.0 mcg) (OR: 0.82, 95% CI: 0.68–0.98, p trend = 0.07), and lutein/zeaxanthin (> 16454.4mcg) (OR: 0.83, 95% CI 0.68 – 0.99, p trend = 0.02).	There was no supplementation. 43.1% cases and 44.5% control reported multivitamin use	Food Frequency Questionnaire (FFQ)	Between 1996 and 2001
Chlebowski *et al.*, 2008, EUA, intervention/case-control	Vitamin D + calcium	36.282 postmenopausal women	No correlation	Supplementation 1000 mg of elemental calcium with 400 IU of vitamin D 3/day	Food Frequency Questionnaire (FFQ) Serum	7 years
Rossi *et al.*, 2009, Italy, case-control	Vitamin D	5.157 women	Intake inversely proportional to the breast cancer's risk. .(Vitamin D intake >3.57 lg or 143IU have protective effect against breast cancer)	There was no supplementation	Food Frequency Questionnaire (FFQ)	June 1991 to April 1994
Abbas *et al.*, 2007, Germany, population-based case-control	Vitamin D Calcium	944 women	Vitamin D intake was inversely associated with premenopausal breast cancer risk(OR 0.50 (95%CI = 0.26–0.96) for the highest intake (≥5 µg/day) vs the lowest (<2 µg/day; Ptrend = 0.02). Dietary calcium intake was not associated with breast cancer	There was no supplementation. Vitamin supplements reported by 25.2% cases and 25.9% controls. Median vitamin D intake:2.51 µg/day Median calcium intake: 894 mg/day	Food Frequency Questionnaire (FFQ)	
Dorjgochoo *et al.*, 2008, Shangai/EUA, population-based case-control	Multivitamin, A, B, C, and E	6.928 women	Decrease breast cancer risk with Vitamin E supplementation in women with low vitamin E dietary intake (OR=0.8; 95% CI, 0.6-0.9).	20.2% of case and control supplemented with any vitamin, 16.8% vitamin E supplentation	Food Frequency Questionnaire (FFQ)	Recruit August 1996-March 1998 (Phase I) and April 2002-February 2005
Lin *et al.*, 2007, EUA, cohort	Vitamin D calcium	31.487 women	Higher intakes of total calcium and vitamin D were moderately associated with a lower risk of premenopausal breast cancer (highest vs lowest quintile of intake HR 0.61 (95%CI, 0.40-0.92) for calcium and HR 0.65 (95% CI, 0.42-1.00) for vitamin D intake.	89.5% were supplementing calcium in the 5th. Quintile and 75.9% were supplementing vitamin D in the 5th. Quintile Mean calcium and vitamin D intake values 1021mg/d and 353IU/d,	Food Frequency Questionnaire (FFQ)	Recruitment 1993 and 1995 10 years of follow-up
Knight *et al.*, 2007, Canada, population-based case-control	Vitamin D	2.107 women	Protective effect associated with sun exposure from ages 10 to 19(OR, 0.65; 95% CI, 0.50-0.85 for the highest quartile of outdoor activities vs the lowest), consumption of cod liver oil use (OR, 0.76; 95% CI, 0.62-0.92) and increasing milk consumption (OR, 0.62 95% CI 0.45-0.86 for >10 glasses/week versus none)	Vitamin D: 15% cases supplemented, and 22% control. Others vitamins: 7% cases and 11% controls	Food Frequency Questionnaire (FFQ)	Recruitment July 1, 2003 and August 31, 2004
Sesso *et al.*, 2005, EUA, cohort e case-control	Carotenoids	39.876 women	Cohort no association with breast cancer. Case-control no association with breast cancer	There was no supplementation. Mean lycopene intake: 9,199 µg/day	Food Frequency Questionnaire (FFQ)	9.9 years of follow-up
Bonilla-Fernández et al, 2003, Mexico, case-control	Vitamin E e Carotenoids	282 women	Vitamin E: protective effect in postmenopausal (highest (23.9 α-Tocopherol equivalent.) vs lower(16.7 α-Tocopherol equivalent.) tertiles intake, OR=0.10, 95%CI=0.02–0.44)	There was no supplementation	Food Frequency Questionnaire (FFQ)	Recruitment 1994 to 1996
Malin et al, 2003, EUA, population-based case-control	Fruits/Vegetables Vitamin E	3.015 women	Vitamin E were inversely associated with breast cancer risk with OR (95%CI) 0.72, (0.54–0.96) to Q4(15.6) and 0.69 (0.50–0.96) to Q5(19.9) vs lowest quintile. No association with breast cancer risk with intake of total carotene, vitamin C, retinol and total vitamin A.	There was no supplementation	Food Frequency Questionnaire (FFQ)	Recruit between August 1996 and March 1998

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