ORIGINAL ARTICLE

VITAMIN A, C, E AND RISK OF BREAST CANCER ACCORDING TO MENOPAUSAL STATUS IN MALAYSIA

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ABSTRACT

Vitamin A, C and E intake has been shown to play a role in the etiology of breast cancer, but the findings have been inconsistent and limited to developed countries with higher cancer incidence. Therefore, the aim of this study is to examine the association of premenopausal and postmenopausal breast cancer risk with vitamin A, C and E intake from dietary sources. This is a population based case-control study conducted in Malaysian population among 382 breast cancer patients and 382 control group. Dietary intake was assessed via an interviewer-administered food frequency questionnaire. Logistic regression was used to compute odds ratios (OR) with 95% confidence intervals (CI) and a broad range of potential confounders were included in analysis. The results of this study shows a significant decreased risk of breast cancer among premenopausal ($OR_{Q4\ to\ Q1}$=0.38, 95% CI, 0.12 – 0.55, p-trend=0.001) and postmenopausal ($OR_{Q4\ to\ Q1}$=0.26, 95% CI, 0.03 – 0.75, p-trend=0.017) women was observed in the highest quartile of beta-carotene intake. Meanwhile, a higher intake of vitamin C showed significantly lowered risk only for premenopausal women ($OR_{Q4\ to\ Q1}$=0.13, 95% CI, 0.03 – 0.32, p-trend=0.001). As a conclusion, beta-carotene intake was independently related to pre- and postmenopausal breast cancer risk, while vitamin C intake was associated with decreased risk among premenopausal women only. However, no association was observed for vitamin A especially retinol and vitamin E intake from dietary sources.

***Keywords**: vitamin A, vitamin C, vitamin E, beta-carotene, retinol, premenopausal, postmenopausal, breast cancer*

INTRODUCTION

Breast cancer incidence in Malaysia is at an Age-Standardized Rate (ASR) of 29.1 per 100,000 populations in year 2007 [1]. According to 2008 GLOBOCAN estimates, the incidence of breast cancer in more developed regions were higher and up to ASR of 66.4 per 100,000 populations compared to less developed regions which only reached ASR of 27.1 per 100,000 populations [2]. Intake of vitamins A, C and E may reduce the hypothesized risk of breast cancer, but the findings are inconsistent [3]. The link between vitamin A, C, E intake and risk of breast cancer is often studied for its antioxidant properties [4]. Vitamin A, which comprises precursors of retinol from animal sources and beta-carotene from plant sources, were involved in the proliferation and cell division of a normal cell [5]. It is also well established for its antioxidant properties that may reduce reactive oxygen species. Besides that, vitamin C has the ability to improve the immunological function and it is necessary in vitamin E metabolism to regenerate vitamin E from the oxidized form [6]. The newly regenerated vitamin E will then serve to neutralize reactive oxygen species. This can directly reduce oxidative DNA damage and genetic mutations. Vitamin E has also been found to induce cancer cells to undergo apoptosis [7].

In the past decade, vitamin A, C and E has gained much attention in relation towards breast cancer risk according to menopausal status, but studies have been limited in developed countries [8-12]. Various tropical fruits, green leafy vegetables, palm olein, soy products including fish, meat, dairy products are rich sources of vitamin A, C, E in Malaysian diet. Some of these dietary sources are rather different especially in types and possibly nutrient composition due to various factors including availability, climate and soil quality than those found in developed countries. Therefore, we investigated associations between vitamin A, C, E intake and risk of breast cancer in a retrospective study of premenopausal and postmenopausal women with a wide range of relevant exposures.

MATERIAL AND METHODS

Study population

This population based case-control study was carried out from January 2006 to December 2007 in

Kuala Lumpur, Malaysia as part of Genetics, Molecular and Proteomic Study of Primary Breast Cancer in Malaysia among women aged 21 to 79 [13]. Information was collected using face-to-face interviews using validated questionnaire including questions about socio-demographic characteristics, medical history, reproductive factors, family history of breast cancer and lifestyle habits. All participants gave written informed consent. This study received approval from the Ethical Committee of Universiti Kebangsaan Malaysia Medical Centre (FF 166-2004).

Ascertainment of breast cancer cases and controls

Cases were women recruited from Hospital Kuala Lumpur (HKL) and Universiti Kebangsaan Malaysia Medical Centre (UKMMC), which were the main referral hospitals for breast cancer cases in Kuala Lumpur, Malaysia. These cases were newly diagnosed with histologically confirmed malignant breast cancer between the study periods. Inclusion criteria for cases were Malaysian women aged between 18 to 80 years, who were not terminally ill (stage IV of cancer) and were diagnosed with first-primary breast cancer. Those who are pregnant, breast feeding and with medical history of other types of cancer besides breast cancer, other terminal diseases or with any type of disability were excluded. Community based controls was recruited at a health screening program carried out at several residential areas around Kuala Lumpur, Malaysia during the same study period. Each control was matched to cases according to their age ± 5 years, ethnicity and menopausal status using a ratio of 1:1. Inclusion and exclusion criteria were the same with cases. The controls had to be free of breast cancer and this had to be confirmed with a current clinical examination by a health professional. All 674 cases which were diagnosed during the study period and 612 controls who attended health screening program were screened for eligibility. Of these women, 523 cases and 517 controls were eligible and met the inclusion criteria. A further 141 cases and 101 controls were excluded due to failure in obtaining informed consent, missing data, implausible caloric intake and left unmatched. Finally, 382 cases and 382 controls were included in statistical analyses with an overall response rate of 73% (382/523) for cases and 74% (382/517) for controls. Data were obtained up to the reference year i.e. the year before diagnosis for cases and the year before recruitment into the study for controls. The mean time interval between diagnosis and interview of cases was 1.8 months, and 92% of cases were interviewed within 3 months of diagnosis. The mean time interval between interview of the index case and the matched control was 3.6 months and 87 % (332) of the 382 case-control pairs were interviewed within 6 months of each other.

Dietary assessment

Food intake was assessed using a validated semi-quantitative food frequency questionnaire (FFQ) for local population as described elsewhere [13,14]. This semi-quantitative FFQ contained 200 food items commonly eaten by the local population in Malaysia and able to capture habitual dietary intake. This FFQ which focused on meals and cooking methods, had three major columns comprising a food item list, frequency of intake and serving size of both raw and cooked foods. Intakes of energy, vitamin A, retinol, beta-carotene, vitamin C and E were computed using Malaysian food composition table [15] and supported by current US Department of Agriculture food composition sources [16]. Dietary supplements intake in the form of vitamin A, C and E and their dose were also recorded. Cases or controls with implausible caloric intake which was defined as less than 1000 kcal or more than 3000 kcal were excluded from the study.

Statistical Analysis

Descriptive statistics were performed to characterize the study group and to examine case-control differences. Relationships between vitamin A, retinol, beta-carotene, vitamin C, E intake and pre- and postmenopausal breast cancer were determined using binary logistic regression to obtain odds ratios (ORs) and the 95% confidence interval (95%, CI) as estimates of relative risks. The dependent variable was incident cases of pre- and postmenopausal breast cancer while the independent variable was the dietary intake. Continuous data of dietary intake were classified according to quartiles of intake from quartile 1 to 4 based on distributions in controls. Tests for linear trend were performed on all ordinal and continuous variables using linear regression analysis producing p-trend values. Two sets of analyses were performed. In the first model, ORs were adjusted only for age and in the second model, multivariate analysis was applied using forced entry method to control for other factors. Analysis included adjustment for age (continuous), other known risk factors and potential confounders that were selected a priori i.e. marital status, education level, working status, household income, age at menarche, age at menopause, parity, age at first childbirth, number of live birth, family history of breast cancer in first-degree relatives, history of breastfeeding, duration of breastfeeding, use of oral contraceptive pills (OCP), use of hormone replacement therapy (HRT), alcohol consumption, physical activity level, body mass index (BMI), use of dietary supplements and energy (kcal) intake. All statistical analysis was done using IBM Statistical Package for Social Sciences (SPSS) for Windows version 20.0.

RESULTS

A total of 382 pairs of cases and controls were identified and matched during the study period. Table 1 summarizes the characteristics of all study participants by case and control group. The mean age of the participants was 49.8 ± 10.6 years for the case group and 49.7 ± 11.2 years for the control groups (p=0.855). Both groups were comparable in terms of mean age, ethnicity and menopausal status as a result of matching done prior to statistical analysis. Both were also similar for household income, age at menopause, history of oral contraceptive pills (OCP) and hormone replacement therapy (HRT) usage, alcohol consumption, smoking habits, physical activity level, weight, height, BMI and waist circumference. Compared with the control group, the case group were somewhat less educated, more likely to be single, widowed, or divorced and homemakers. The case group had menarche at a younger age, fewer numbers of live births, was older at first childbirth, was more likely to have had a family history of breast cancer and was breastfed for a shorter duration.

Table 1: Selected characteristics of the study participants

Variables	Cases (n=382)		Controls (n=382)		p-value [a]
Age at recruitment (years), mean (SD) [b]	49.8	(10.6)	49.7	(11.2)	0.855
Ethnicity, n (%)					
Malay	191	(50.0)	191	(50.0)	
Chinese	145	(38.0)	145	(38.0)	
Indian	46	(12.0)	46	(12.0)	1.000
Education level, n (%)					
No formal education	34	(8.9)	58	(15.2)	
Primary	130	(34.0)	119	(31.2)	
Secondary	164	(43.0)	118	(30.9)	
Tertiary	54	(14.1)	87	(22.7)	<0.0001*
Marital status, n (%)					
Never married	39	(10.2)	18	(4.7)	
Married	282	(73.8)	330	(86.4)	
Widowed/ divorced	61	(16.0)	34	(8.9)	<0.0001*
Working status, n (%)					
Housewife	229	(59.9)	201	(52.6)	
Employed	153	(40.1)	181	(47.4)	0.041*
Household income (RM), mean (SD)	2924	(3146)	3025	(3416)	0.669
Age at menarche (years), mean (SD)	13.3	(1.6)	13.5	(1.8)	0.019*
Postmenopausal, n (%)	166	(43.4)	166	(43.4)	1.000
Age at menopause (years), mean (SD) [c]	50.6	(4.0)	50.1	(3.8)	0.270
Number of live births, mean (SD)	2.8	(2.1)	3.6	(2.1)	<0.0001*
Age at first childbirth (years), mean (SD) [d]	25.5	(4.9)	24.2	(4.7)	0.001*
Family history of breast cancer, n (%) [e]	53	(13.9)	13	(3.4)	<0.0001*
Breastfeeding (months), mean (SD)	5.7	(7.9)	7.7	(11.7)	0.005*
OCP – ever, n (%) [f]	113	(29.6)	115	(30.1)	0.874
HRT – ever, n (%) [f]	14	(3.7)	11	(2.9)	0.359
Alcohol – ever, n (%) [f]	21	(5.5)	26	(6.8)	0.452
Smoking – ever, n (%) [f]	10	(2.6)	3	(0.8)	0.062
Physical activity – sedentary, n (%) [g]	163	(42.6)	151	(39.5)	0.631
Weight (kg), mean (SD)	61.3	(12.3)	61.1	(11.4)	0.757
Height (cm), mean (SD)	154.9	(5.8)	154.9	(5.4)	0.998
Body mass index (kg/m^2), mean (SD)	25.6	(5.2)	25.5	(4.9)	0.801
Waist circumference (cm), mean (SD)	84.3	(11.1)	82.3	(9.8)	0.725

*[a] All p-values are univariate and were derived using the Student's t-test for continuous variables and the Chi-square test for categorical variables, * Significant difference, p value <0.05, [b] SD, standard deviation, [c] Among postmenopausal women, [d] Among parous women, [e] Positive among first degree relatives only, [f] Regular consumption or use, [g] Light physical activity less than once a week.*

Multivariate OR for the association between vitamin A, C, E, and breast cancer risk according to menopausal status is shown in Table 2. The median and inter-quartile cut off points were 652.3 (509.9, 804.3) µg/day for vitamin A, 292.1 (195.9, 440.7) µg/day for retinol, 2005.9 (1276.8, 2868.4) µg/day for beta-carotene, 85.0 (59.2, 128.9) mg/day for vitamin C and 9.1 (7.2, 10.9) mg/day for vitamin E intake. Compared with premenopausal women in the lowest quartile of vitamin A intake (Q1), those in the highest quartile (Q4) had no indication of significant decreased risk of breast cancer ($OR_{Q4\ to\ Q1}$=0.65, 95% CI, 0.28 – 1.50, p-trend=0.346). Similarly, the same trend was observed between retinol intake and premenopausal breast cancer risk ($OR_{Q4\ to\ Q1}$=1.96, 95% CI, 0.79 – 4.87, p-trend=0.118). Among postmenopausal women, the same trend was observed between vitamin A intake ($OR_{Q4\ to\ Q1}$=0.79, 95% CI, 0.23 – 2.65, p-trend=0.196)and retinol intake ($OR_{Q4\ to\ Q1}$=1.79, 95% CI, 0.43 – 2.49, p-trend=0.140) with breast cancer risk. However, a decreased risk of pre- and postmenopausal breast cancer was observed with higher intake of beta-carotene from food sources. A significant 62% reduction for risk of breast cancer was observed among premenopausal women ($OR_{Q4\ to\ Q1}$=0.38, 95% CI, 0.12 – 0.55, p-trend<0.001) and 74% reduction for risk of breast cancer was observed among postmenopausal women ($OR_{Q4\ to\ Q1}$=0.26, 95% CI, 0.03 – 0.75, p-trend=0.017) in the highest quartile of beta-carotene intake compared to those in lowest quartile of intake. As for vitamin C intake the protective effect towards breast cancer was seen only among premenopausal women ($OR_{Q4\ to\ Q1}$=0.13, 95% CI, 0.03 – 0.32, p-trend<0.001) but not among postmenopausal women in the highest quartile of vitamin C intake compared to those in lowest quartile of intake. The risk reduction effect was also not observed with higher vitamin E intake among both premenopausal women ($OR_{Q4\ to\ Q1}$=0.66, 95% CI, 0.26 – 1.67, p-trend=0.311) and postmenopausal women ($OR_{Q4\ to\ Q1}$=0.62, 95% CI, 0.16 – 1.83, p-trend=0.072) in the current study.

DISCUSSION

This study found no significant association between vitamin A, retinol and vitamin E intake with pre- and postmenopausal breast cancer risk. However, higher intake of beta-carotene was seen to be protective towards risk of breast cancer among pre- and postmenopausal women. Besides that, premenopausal women who were consuming higher intake of vitamin C also demonstrated to have a reduced risk of breast cancer. Interestingly, the same protective effect of vitamin C was not observed among postmenopausal women in the current study.

The finding of no association between vitamin A intake in the highest quartile (more than 804 mg per day) with breast cancer risk in our study is consistent with most studies which found that vitamin A intake in the highest quintile of more than 4000 mg per day showed no significant reduction in pre- and postmenopausal breast cancer risk [12,17,18]. Nevertheless, the results of a case control study in the United States that found that taking vitamin A was 2309 mg per day may reduce the risk of premenopausal breast cancer significantly by 18% (OR = 0.82; 95% CI, 0.68-0.98) [19]. This is supported by results of a meta-analysis study which found that higher intake of vitamin A could potentially reduce the risk of breast cancer significantly by 12% (OR = 0.84; 95% CI, 0.74-0.95) among premenopausal, but not postmenopausal women [9]. The failure to prove an association between vitamin A intake and breast cancer risk in the current study might be due to lower exposure (lower intake of vitamin A) among Malaysian women compared to other studies in developed country. This might have contributed to the non-significant association between vitamin A intake and pre- and postmenopausal breast cancer risk. Previous local study in Malaysia has also failed to prove the existence of an association between vitamin A and breast cancer risk [20].

Further analysis has also been done on the association of breast cancer risk in pre- and postmenopausal precursor of vitamin A intake i.e. retinol and beta carotene intake in the current study. This study found those pre- and postmenopausal women consuming retinol from diet in the highest quartile were not affected with breast cancer risk compared with the lowest quartile of intake. This is consistent with previous reports from a case control in China [18] and a meta-analysis study involving 20 studies [9] which found no significant association of retinol intake in the highest quintile of greater than 2000 mg per day with risk pre- and postmenopausal breast cancer. Conversely, beta carotene intake in the highest quartile compared to the lowest quartile of more than 2868 mg per day has been found to reduce significantly the risk of breast cancer by 62% among premenopausal women and 74% among postmenopausal women in the current case-control study in Kuala Lumpur. Although beta-carotene intake was low in this study compared to other reports, the risk reducing effect of premenopausal breast cancer is consistent with findings by previous studies [11,19]. Beta-carotene intake of 5686 mg per day was able to significantly reduce the risk of Chinese premenopausal breast cancer by 19% (OR = 0.81; 95% CI, 0.68-0.98) [19]. Premenopausal women who were consuming higher beta-carotene and exposed to second-hand smoke was found to have a reduced risk of breast cancer by 68% in another study in China (OR = 0·38; 95 % CI, 0·26-0·52) [11]. However, other studies find no significant association between beta-carotene and the risk of premenopausal breast cancer [8,17,18,21].

Table 2: Multivariate OR for the association between Vitamin A, C, E and breast cancer risk according to menopausal status

	Quartiles of intake				p trend
	1	2	3	4	
Premenopausal					
Vitamin A					
Case/ Control	52/54	52/54	56/54	56/54	
Median (IQR), (µg)	445 (376, 479)	591 (543, 626)	709 (685, 759)	961 (873, 1217)	
OR[a] (95% CI)	1.00	1.00 (0.49 – 2.02)	1.07 (0.50 – 1.96)	1.08 (0.41 – 1.56)	0.343
OR[b] (95% CI)	1.00	0.82 (0.36 – 1.86)	0.76 (0.32 – 1.75)	0.65 (0.28 – 1.50)	0.346
Retinol					
Case/ Control	33/54	39/54	74/54	70/54	
Median (IQR), (µg)	163 (109, 180)	248 (225, 266)	361 (324, 396)	543 (487, 640)	
OR[a] (95% CI)	1.00	1.19 (0.49 – 2.86)	2.24 (1.23 – 5.87)	2.11 (0.96 – 4.51)	0.090
OR[b] (95% CI)	1.00	1.40 (0.53 – 3.63)	2.47 (1.01 – 6.01)	1.96 (0.79 – 4.87)	0.118
Beta-carotene					
Case/ Control	67/54	74/54	48/54	27/54	
Median (IQR), (µg)	850 (567, 1111)	1622 (1451, 1809)	2308 (2178, 2566)	3464 (3103, 3950)	
OR[a] (95% CI)	1.00	1.10 (0.69 – 2.81)	0.72 (0.32 – 1.46)	0.40 (0.14 – 0.64)	< 0.001*
OR[b] (95% CI)	1.00	1.77 (0.80 – 3.89)	0.97 (0.40 – 2.33)	0.38 (0.12 – 0.55)	< 0.001*
Vitamin C					
Case/ Control	80/54	64/54	44/54	28/54	
Median (IQR), (µg)	45.8 (34.7, 53.9)	70.4 (63.1, 78.0)	102.6 (94.5, 115.8)	163.3 (145.1, 178.6)	
OR[a] (95% CI)	1.00	0.79 (0.27 – 1.18)	0.53 (0.14 – 0.75)	0.35 (0.02 – 0.68)	< 0.001*
OR[b] (95% CI)	1.00	0.50 (0.21 – 1.15)	0.25 (0.10 – 0.62)	0.13 (0.03 – 0.32)	< 0.001*
Vitamin E					
Case/ Control	46/54	69/54	56/54	45/54	
Median (IQR), (µg)	6.1 (5.3, 6.7)	8.2 (7.8, 8.7)	9.9 (9.6, 10.3)	11.8 (11.2, 13.2)	
OR[a] (95% CI)	1.00	1.50 (0.88 – 3.49)	1.22 (0.51 – 2.05)	0.98 (0.40 – 1.76)	0.187
OR[b] (95% CI)	1.00	1.21 (0.55 – 2.67)	0.90 (0.39 – 2.08)	0.66 (0.26 – 1.67)	0.311
Postmenopausal					
Vitamin A					
Case/ Control	41/42	49/41	39/41	37/42	
Median (IQR), (µg)	425 (360, 472)	587 (542, 622)	723 (676, 778)	1019 (868, 1223)	
OR[a] (95% CI)	1.00	1.20 (0.61 – 2.76)	0.95 (0.25 – 1.93)	0.91 (0.31 – 2.57)	0.495
OR[b] (95% CI)	1.00	1.11 (0.44 – 2.78)	0.63 (0.20 – 2.31)	0.79 (0.23 – 2.65)	0.196
Retinol					
Case/ Control	31/42	36/41	54/41	45/42	
Median (IQR), (µg)	145 (113, 177)	246 (216, 268)	343 (323, 386)	534 (466, 676)	
OR[a] (95% CI)	1.00	1.17 (0.46 – 2.80)	1.74 (1.32 – 2.78)	1.45 (0.52 – 2.87)	0.237
OR[b] (95% CI)	1.00	1.58 (0.53 – 2.71)	2.03 (1.13 – 2.44)	1.76 (0.43 – 2.49)	0.140
Beta-carotene					
Case/ Control	50/42	48/41	38/41	30/42	
Median (IQR), (µg)	896 (649, 1127)	1573 (1436, 1883)	2263 (2163, 2499)	3506 (3100, 3908)	
OR[a] (95% CI)	1.00	0.96 (0.13 – 1.48)	0.76 (0.10 – 0.96)	0.61 (0.16 – 0.97)	0.012*
OR[b] (95% CI)	1.00	0.36 (0.10 – 1.28)	0.30 (0.08 – 1.13)	0.26 (0.03 – 0.75)	0.017*
Vitamin C					
Case/ Control	48/42	49/41	38/41	31/42	
Median (IQR), (µg)	41.5 (31.4, 52.3)	71.0 (63.4, 79.5)	99.2 (90.7, 108.1)	156.6 (143.7, 182.2)	
OR[a] (95% CI)	1.00	1.02 (0.21 – 1.62)	0.79 (0.22 – 1.92)	0.65 (0.18 – 1.09)	0.054
OR[b] (95% CI)	1.00	0.82 (0.22 – 2.29)	0.62 (0.16 – 2.31)	0.54 (0.15 – 1.44)	0.050
Vitamin E					
Case/ Control	37/42	51/41	46/41	32/42	
Median (IQR), (µg)	6.1 (5.3, 6.9)	8.2 (7.7, 8.5)	9.7 (9.4, 10.3)	12.1 (11.4, 12.9)	
OR[a] (95% CI)	1.00	1.38 (0.52 – 2.93)	1.24 (0.96 – 2.09)	0.85 (0.35 – 2.09)	0.215
OR[b] (95% CI)	1.00	0.93 (0.33 – 2.62)	1.09 (0.35 – 2.37)	0.62 (0.16 – 1.83)	0.072

OR = Odds Ratio, CI = Confidence Interval; Logistic regression analysis, Method = Enter, Contrast = Simple

[a] *Adjusted for age (continuous),*

[b] *Adjusted for age (continuous), ethnicity, marital status, education, working status, household income, age of menarche, age of menopause, pregnancy history, age at first childbirth, number of live birth, history of breastfeeding, duration of breastfeeding, history of oral contraceptive usage, history of hormone replacement therapy usage, smoking habits, alcohol consumption, physical activity level, family history of breast cancer, body mass index (BMI), use of dietary supplements and energy intake.*

* *Significant trend (Linear regression analysis, p-trend value <0.05)*

Despite that, most previous epidemiological studies failed to find evidence on the protective effect of beta-carotene towards risk of postmenopausal breast cancer [8,18,19,21]. This is inconsistent with findings from the current study in Kuala Lumpur which uniquely found that beta-carotene intake exceeding 2868 mg per day might significantly reduce risk of postmenopausal breast cancer. However, one recent prospective study in Netherlands found a low intake of beta-carotene was associated with a two-fold increased risk of breast cancer among postmenopausal women smokers (HR = 2.31; 95% CI, 1.12-4.76) [12]. This is in line with a report that combined the results of 18 prospective studies with a maximum follow-up of 27 years which found that consuming beta-carotene could significantly reduce the risk of breast cancer by 16% (RR = 0.84; 95% CI, 0.77-0.93) among women with estrogen receptor negative (ER-) but did not have any effect on women with estrogen receptor (ER+) [22]. When comparing the relationship between carotenoid intake and risk of breast cancer in previous reports, a meta-analysis found that the effect of risk reduction is more evident when carotenoid consumption is measured as biomarkers in blood composition compared to those assessed through questionnaires [23]. Therefore, when assessing the relationship between vitamin A and the risk of breast cancer, the use of specific and sensitive biomarkers should be highlighted in order to avoid inconsistent findings besides looking into their estrogen hormone receptor status.

The findings of 87% breast cancer risk reducing effects of vitamin C intake among premenopausal found in the current study contradicts with most epidemiological studies which showed no significant association [8,9,17,18,21]. This might be due a high intake of vitamin C reported by the women involved in the current study from rich vitamin C sources of tropical fruits. In contrast, the same risk reducing effect was not observed among postmenopausal women in the current study which is consistent with findings from most epidemiological study [8,9,12,18,21]. A case-control study by UK Dietary Cohort Consortium, which uses robust data collection techniques through a food diary for seven days, also found there is no association between vitamin C intake risk of postmenopausal breast cancer [10].

There is no significant association found between vitamin E intake and risk of pre- and postmenopausal breast cancer in the current study. This is consistent with all previous studies ever carried out among pre- and postmenopausal women which failed to obtain significant findings for the association of vitamin E intake and breast cancer risk according to menopausal status [8,9,12,17,18,21]. The hypothesis on the inverse association between vitamin E and breast cancer risk has been touted by earlier results from laboratory studies using breast cancer cells, but such studies also has not yielded consistent evidence to indicate chemopreventive effects against breast cancer [24].

The current study result implies that more work should be done in promoting beta-carotene and vitamin C intake from fruits and vegetables for prevention of breast cancer risk in Malaysia. Reaching out to targeted communities in increasing fruit and vegetable consumption is a major public health challenge at the moment. There are various reasons why different populations tend to shy away from fruits and vegetables which include cost, convenience, taste, knowledge and stage of readiness to change [25]. But as science increasingly supports the need for people to consume more produce, national health agencies and industry representatives should be working together to address these obstacles and discuss ways to boost fruit and vegetable consumption in Malaysia.

The results of our study must be interpreted in the light of possible biases that case-control studies are subject to. There is a potential for selection bias in this study attributed to the method used in recruiting the controls. Sampling a community based control is accepted as an appropriate comparison group for the cases without increasing the cost and feasibility of data collection in the current study. Furthermore, the current study which has been conducted in Kuala Lumpur, the capital of Malaysia, where the socioeconomic and education status are higher compared to rural areas, might has influenced the results and could not be generalized for all population. The moderate response rate among both cases and controls might contribute to difference in characteristics among respondents and non-respondents, which were not investigated in this current study. Nutrition data on adult females are known to reflect minor changes in cancer risk and they are probably related to cancer promotion instead of initiation. Moreover, different molecular forms of breast cancer and their genetics background might help to explain the variation in findings of the relation between diet and breast cancer [26,27]. Unfortunately, no data as such is available in this current study. Including molecular data specifically subgroups of breast cancer to study their relationship with diet would be novel and great importance but this would require more patients and controls to be included in this study.

CONCLUSION

As a conclusion, beta-carotene intake was independently related to pre- and postmenopausal breast cancer risk after controlling for age, other breast cancer risk factors and energy intake. The significant association between vitamin C and breast cancer risk was limited only among premenopausal women. No association was observed for vitamin A, retinol and vitamin E

intake. This evidence is important to enrich current knowledge on the relationship between diet and breast cancer for early prevention. Nonetheless, further evaluation on the roles of specific carotenoids on their association with breast cancer risk in this region is warranted.

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