

## RESEARCH COMMUNICATION

# Fat Intake and Its Relationship with Pre- and Postmenopausal Breast Cancer Risk: a Case-control Study in Malaysia

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### Abstract

**Background:** Fat intake has been shown to play a role in the etiology of breast cancer, but the findings have been inconsistent. **Objective:** To assess the association of premenopausal and postmenopausal breast cancer risk with fat and fat subtypes intake. **Methodology:** This is a population based case-control study conducted in Kuala Lumpur, Malaysia from January 2006 to December 2007. Food intake pattern was collected from 382 breast cancer patients and 382 control group 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 was included in analysis. **Results:** This study showed that both premenopausal and postmenopausal breast cancer risk did not increase significantly with greater intake of total fat [quartile (Q) 4 versus Q1 OR=0.76, 95% CI, 0.23-2.45 and OR=1.36, 95% CI, 0.30-3.12], saturated fat (ORQ4 to Q1=1.43, 95% CI, 0.51-3.98 and ORQ4 to Q1=1.75, 95% CI, 0.62-3.40), monounsaturated fat (ORQ4 to Q1=0.96, 95% CI, 0.34-1.72 and ORQ4 to Q1=1.74, 95% CI, 0.22-2.79), polyunsaturated fat (ORQ4 to Q1=0.64, 95% CI, 0.23-1.73 and ORQ4 to Q1=0.74, 95% CI, 0.39-1.81), n-3 polyunsaturated fat (ORQ4 to Q1=1.10, 95% CI, 0.49-2.48 and ORQ4 to Q1=0.78, 95% CI, 0.28-2.18), n-6 polyunsaturated fat (ORQ4 to Q1=0.67, 95% CI, 0.24-1.84 and ORQ4 to Q1=0.71, 95% CI, 0.29-1.04) or energy intake (ORQ4 to Q1=1.52, 95% CI, 0.68-3.38 and ORQ4 to Q1=2.21, 95% CI, 0.93-3.36). **Conclusion:** Total fat and fat subtypes were not associated with pre- and postmenopausal breast cancer risk after controlling for age, other breast cancer risk factors and energy intake. Despite the lack of association, the effects of total fat and fat subtypes intake during premenopausal years towards postmenopausal breast cancer risk still warrant investigation.

**Key words:** Breast cancer - premenopausal - postmenopausal - total fat - mono-unsaturated - polyunsaturated

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### Introduction

The incidence rates of breast cancer in Asian countries are increasing at a more rapid rate than in Western countries, although the incidence rate remains low (Yip 2009). Most countries in Asia are progressing towards industrialization and economic development and at the same time adopting the lifestyle and dietary pattern of the developed countries. Breast cancer incidence in Malaysia is at an Age-Standardized Rate (ASR) of 39.3 per 100,000 populations in year 2006 compared to Singapore which has a higher ASR at 54.9 per 100,000 populations (Omar et al. 2008; Jara-Lazaro

et al. 2010). Singapore, being a developed country also has one of the highest increasing incidence trends in the world with 5.7% per year in premenopausal women and 3.9% per year in postmenopausal women, in contrast to only 1.5% per year in the United States. However, the incidence in Japan has remained low despite the fact that it is a developed country, and this could be related to adherence of traditional low fat, high n-3 polyunsaturated fat and other components of healthy dietary intakes (Minami et al. 2004).

The association between dietary fat and breast cancer has been studied for a long time, but it remains one of the most controversial in nutritional epidemiology

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(Gerber 2009). International correlation studies have shown that there is a strong relationship between dietary fat and mortality rate of breast cancer (Rose et al. 1986). They were supported by evidence from animal experiments which shows animal fat were related to increased risk while olive oil rich diet were associated with reduced breast cancer risk (Welsch 1995). Migrant studies have shown that migrants who replaced their traditional low fat diet with a Western diet, which is high in fat, experienced similar breast cancer incidence rates to their host populations (Nelson 2006). WCRF/AICR (2007) based on studies conducted worldwide on diet and breast cancer reports that the relationship between total fat and postmenopausal breast cancer was suggestive of increased risk, but with limited evidence. No evidence was seen between premenopausal breast cancer and total fat intake. Women's Health Initiative Study showed a risk reduction of postmenopausal breast cancer with a low fat diet, although the findings were fairly significant (Prentice et al. 2006).

Hormone metabolism is the fundamental prominent factor for breast cancer with sources of major risk factor originating from high endogenous or exogenous estradiol (Key 2002). Breast cancer risk varies with changes in hormonal status by influencing the differentiation of the mammary epithelium, which was further characterized by different vulnerability states to endogenous and exogenous carcinogens. Analysis of risk factors including dietary intakes stratified according to menopausal status might help us understand more about the complex relationship between dietary fat and hormone related cancer as breast cancer. Therefore, this study was aimed to determine the associations between fat and fat subtypes intake and breast cancer risk among premenopausal and postmenopausal women in Kuala Lumpur, Malaysia.

## Materials and Methods

### Subjects

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 (IRPA 09-02-02-009 BTK/ER/37). The study received Ethic approval from the Universiti Kebangsaan Malaysia Ethics Committee (FF 166-2004). Cases were women recruited from Hospital Kuala Lumpur (HKL) and Universiti Kebangsaan Malaysia Medical Centre (UKMMC), which were one of 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. All breast cancer patients registered and diagnosed during the study period i.e. 674 cases were identified and screened for eligibility. Of these women, 151 did not meet the inclusion criteria with 19 being non-Malaysian, 8 not meeting the age requirement, 37 having recurrent breast cancer, 6 with secondary breast cancer, 75 who were terminally ill with breast cancer stage IV and 6 were deaf, blind or physically impaired. Out of 523 eligible cases, 89 refused to take part for personal reasons. The remaining 434 cases agreed to participate in the study and provided informed consent. Then, 15 cases were excluded from the study due to incomplete data on risk factors as they refused to answer several questions. Another 37 cases with implausible calorie intake were also excluded to maintain the quality of data. Finally, 382 cases were included in statistical analyses with an overall response rate of 73% (382/523).

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  $\pm$  5 years, ethnicity and menopausal status using a ratio of 1:1. Premenopausal is defined as the phase before the permanent cessation of menses and they still have normal or irregular menstrual period while postmenopausal is defined as the phase after the permanent cessation of menses. 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. Of the 612 controls who attended the health screening program, 95 did not meet the inclusion criteria due to nationality (n=9), age (n=3), personal history of cancer (n=14), pregnancy (n=27), breastfeeding (n=39) or disability (n=3). 517 eligible controls were approached to obtain informed consent but 34 of them did not participate due to personal reasons. From the remaining 483 control, a total of 101 were excluded from statistical analysis due to incomplete data (n=12), implausible caloric intake (n=54) or left unmatched with cases (n=35). Finally, 382 controls were included in the final analysis with an overall response rate of 74% (382/517).

### Data Collection

Data for this study was collected using face-to-face interviews with a pilot tested questionnaire including questions about socio-demographic characteristics, medical history, reproductive factors, family history of breast cancer, lifestyle habits (use of hormones, smoking and alcohol consumption) and current weight and height to calculate body mass index. Food intake was assessed using a validated semi-quantitative food frequency questionnaire (FFQ) for local population (Shahril et al. 2008). 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. The interviews were conducted by two trained interviewers and the same interviewer interviewed all matched cases and control where ever possible. All 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. 87 % (332) of the 382 case-control pairs were interviewed within 6 months of each other.

#### *Semi-quantitative food frequency questionnaire*

The semi-quantitative FFQ contained 200 food items commonly eaten by the local population in Malaysia. This FFQ had three major columns comprising a food item list, frequency of intake and serving size of both raw and cooked foods. The FFQ also focused more on meals and their cooking method compared to other previously developed FFQ for Malaysian. A standardized recipe was assigned to each cooked food using data on food recipes collected in the FFQ development process. The food items and servings were also categorized according to three main mealtimes consisting of breakfast (e.g. milk, tea, bread, nasi lemak (coconut based rice), fried noodles, chapatti and etc), lunch or dinner (e.g. rice, chicken curry, fried fish with chili, fruits, vegetables, beverages and etc) and morning or afternoon snacks (pisang goreng (banana fritter), curry puff, traditional kuih (Malaysian local delicacies), biscuits and etc). In addition, seven food groups were added to the FFQ for cross checking purposes. These allowed the interviewer to check the estimate intake of poultry, meat, fish, organ meats, seafood, vegetables and fruits. Questions on types of cooking fats or oils used were asked and adjusted manually in the FFQ template worksheet, which originally uses palm olein as the standard cooking oil. Subjects were asked to estimate how often on average they had taken the food items or servings per day or week or month or year over the previous year. Each food item and serving was assigned a portion size using local household units. The portion size was standardized using previous data from the same population which was then weighed using a digital kitchen scale to compile a list of portion size with their respective weight (in gram). Therefore, respondents have to estimate the portion size taken relative to given portion size with the aid of a local household measurement photograph. Approximately 15 minutes were taken to conduct each interview and the responses were then analyzed statistically using a food composition database (Suhaina et al. 2006). The food composition database was developed using the Malaysian Food Composition Table (Tee et al. 1997) as the main reference for energy, macronutrients and

vitamin A and C. Data from McCance and Widdowson's The Composition of Foods (Food Standards Agency 2002) were borrowed for fatty acids and vitamin E composition of raw food items. Meanwhile for cooked food, fatty acids composition data was derived from the Singapore Food Facts (Ministry of Health Singapore 1999). Data on fatty acids composition for cooking oil and fat were obtained from O'Brien (1998). Chemical analysis of raw foods such as marine and freshwater fish, nuts, legumes, coconut milk and several prepared Malaysian dishes using standardized recipe were carried out to support the food composition database (Suhaina 2004).

#### *Statistical Analysis*

Descriptive statistics were performed to characterize the study group and to examine case-control differences. The differences were assessed using chi-square ( $\chi^2$ ) test for categorical variables and t-test for differences in means. All p-values are two sided and a p-value less than 0.05 is considered as statistically significant. Analysis was done using Statistical Package for Social Sciences (SPSS) for Windows version 16.0 (SPSS Inc., Chicago, IL). Relationships between fat and fat subtypes 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. Cut off values were presented in Table 1. 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) and energy (kcal) intake.

## **Results**

Table 2 summarizes the characteristics of all study subjects by case and control group. The mean age of the subjects was  $49.8 \pm 10.6$  years for the case group and  $49.7 \pm 11.2$  years for the control - groups ( $p=0.855$ ). Both groups were comparable in terms of mean age,

**Table 1. Cut-off Values for Energy Intake, Total Fat and Fat Subtypes According to Quartiles (Q) of Intakes**

Nutrients	Q1	Q2	Q3	Q4
Energy (kcal/day)	< 1512	1512 - 1624	1624 - 1855	> 1855
Protein (g/day)	< 58.4	58.4 - 66.1	66.1 - 77.3	> 77.3
Carbohydrate (g/day)	< 212.5	212.5 - 235.5	235.5 - 264.1	> 264.1
Total fat (g/day)	< 43.7	43.7 - 50.2	50.2 - 58.0	> 58.0
Saturated fat (g/day)	< 18.9	18.9 - 22.3	22.3 - 26.1	> 26.1
Monounsaturated fat (g/day)	< 15.4	15.4 - 17.6	17.6 - 20.5	> 20.5
Polyunsaturated fat (g/day)	< 5.8	5.8 - 7.1	7.1 - 8.8	> 8.8
n-3 polyunsaturated fat (g/day)	< 0.41	0.41 - 0.53	0.53 - 0.69	> 0.69
ALA (g/day)	< 0.10	0.10 - 0.16	0.16 - 0.23	> 0.23
EPA (g/day)	< 0.05	0.05 - 0.07	0.07 - 0.12	> 0.12
DHA (g/day)	< 0.17	0.17 - 0.26	0.26 - 0.38	> 0.38
n-6 polyunsaturated fat (g/day)	< 5.4	5.4 - 6.7	6.7 - 8.2	> 8.2

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

**Table 2. Selected Characteristics of the Study Subjects**

Variables	Cases(n=382)		Controls(n=382)		p-value <sup>a</sup>
Age at recruitment (years), mean (SD) <sup>b</sup>	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) <sup>c</sup>	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) <sup>d</sup>	25.5	(4.9)	24.2	(4.7)	0.001*
Family history of breast cancer, n (%) <sup>e</sup>	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 (%) <sup>f</sup>	113	(29.6)	115	(30.1)	0.874
HRT - ever, n (%) <sup>f</sup>	14	(3.7)	11	(2.9)	0.359
Alcohol - ever, n (%) <sup>f</sup>	21	(5.5)	26	(6.8)	0.452
Smoking - ever, n (%) <sup>f</sup>	10	(2.6)	3	(0.8)	0.062
Physical activity - sedentary, n (%) <sup>f</sup>	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 <sup>2</sup> ), 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

<sup>a</sup>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; <sup>b</sup>SD, standard deviation; <sup>c</sup>Among postmenopausal women; <sup>d</sup>Among parous women; <sup>e</sup>Positive among first degree relatives only; <sup>f</sup>Regular consumption or use; <sup>g</sup>Light physical activity less than once a week; \*Significant difference, p value <0.05

**Table 3. Mean Macronutrients Intake among Pre- and Postmenopausal Breast Cancer Cases and Controls**

Macronutrients	Premenopausal			Postmenopausal		
	Cases (n=216)	Controls(n=216)	p value	Cases (n=166)	Controls(n=166)	p value
Energy (kcal/day)	1756 ± 234 (1258 – 2379)	1759 ± 263 (1299 – 2512)	0.920	1753 ± 249 (1420 – 2481)	1626 ± 22 (1302 – 2420)	<0.001*
Protein (g/day)	68.5 ± 11.5 (41.8 – 91.6)	69.8 ± 12.5 (43.1 – 102.4)	0.378	68.9 ± 10.2 (48.9 – 90.5)	65.2 ± 13.5 (39.5 – 118.2)	0.034*
Carbohydrate (g/day)	247.9 ± 32.2 (188.9 – 328.5)	248.1 ± 39.1 (167.9 – 363.6)	0.973	252.0 ± 37.5 (186.6 – 393.2)	234.2 ± 36. (177.0 – 353.9)	0.001*
Total fat (g/day)	54.5 ± 11.0 (26.8 – 85.7)	54.2 ± 12.2 (24.2 – 89.1)	0.831	52.2 ± 10.9 (31.2 – 81.7)	47.6 ± 10.1 (24.0 – 84.1)	0.003*
Saturated fat (g/day)	24.5 ± 5.0 (12.0 – 38.1)	24.3 ± 5.8 (9.7 – 39.8)	0.803	23.1 ± 5.2 (12.2 – 36.5)	20.9 ± 4.4 (10.7 – 35.8)	0.002*
Monounsaturated fat (g/day)	19.0 ± 3.9 (9.5 – 31.3)	19.1 ± 4.4 (7.3 – 32.3)	0.857	18.3 ± 3.9 (10.1 – 29.1)	16.7 ± 3.7 (7.7 – 29.7)	0.007*
Polyunsaturated fat (g/day)	7.7 ± 2.1 (3.5 – 16.2)	7.5 ± 1.9 (3.2 – 13.5)	0.484	7.5 ± 2.0 (3.6 – 15.9)	7.0 ± 2.0 (2.4 – 12.7)	0.152
n-3 polyunsaturated fat (g/day)	0.57 ± 0.21 (0.20 – 1.30)	0.57 ± 0.23 (0.09 – 1.45)	0.927	0.55 ± 0.27 (0.11 – 1.96)	0.53 ± 0.21 (0.08 – 1.20)	0.529
ALA (g/day)	0.21 ± 0.15 (0.05 – 1.09)	0.18 ± 0.12 (0.03 – 1.03)	0.196	0.20 ± 0.19 (0.04 – 1.43)	0.17 ± 0.09 (0.04 – 0.53)	0.198
EPA (g/day)	0.08 ± 0.04 (0.00 – 0.24)	0.09 ± 0.05 (0.01 – 0.34)	0.336	0.08 ± 0.04 (0.00 – 0.24)	0.08 ± 0.05 (0.01 – 0.29)	0.786
DHA (g/day)	0.27 ± 0.11 (0.00 – 0.61)	0.29 ± 0.14 (0.01 – 0.69)	0.235	0.27 ± 0.12 (0.02 – 0.63)	0.28 ± 0.14 (0.02 – 0.75)	0.717
n-6 polyunsaturated fat (g/day)	7.2 ± 2.0 (3.4 – 15.1)	7.0 ± 1.8 (1.9 – 13.1)	0.415	7.0 ± 1.8 (3.7 – 14.3)	6.6 ± 1.9 (2.6 – 12.4)	0.127

ALA, Alpha-linolenic acid; EPA, Eicosapentaenoic; DHA, Docosahexaenoic; Values presented as mean ± standard deviation (range); \*Significant difference (t test, p value <0.05)

history of breast cancer and was breastfed for a shorter duration.

Among premenopausal women, both the case group and the control group were consuming similar amount of calories, carbohydrates, protein and total fat in their diet (Table 3). Postmenopausal cases were consuming significantly higher amount of calories (1753 kcal/day vs. 1626 kcal/day), carbohydrates (252.0 g/day vs. 234.2 g/day), protein (68.9 g/day vs. 65.2 g/day) and total fat (52.2 g/day vs. 47.6 g/day) compared to their controls (p<0.05). In the current study population, the range of energy contribution for total fat intake is from 13.6% to 37.1% with an average of 27% from energy intake. As for fat subtypes, pre- and postmenopausal cases' intake of saturated fat, monounsaturated fat, polyunsaturated fat, n-3 and n-6 polyunsaturated fat, alpha linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) intakes were similar to their respective control groups except for saturated fat and monounsaturated fat intake among postmenopausal group. Intakes of saturated fat (23.1 g/day vs. 20.9 g/day) and monounsaturated fat (18.3 g/day vs. 16.7 g/day) among postmenopausal cases were significantly higher compared to control group. Average distribution of saturated, monounsaturated and polyunsaturated fat from energy intake were 13%, 10% and 4% respectively. Of the 4% polyunsaturated fat, 0.3% is from n-3 polyunsaturated fat while 3.7% is from n-6 polyunsaturated fat.

Table 4 presents the multivariate odds ratio analysis for premenopausal breast cancer risk among

216 cases matched to 216 controls. Compared with premenopausal women in the lowest quartile of intake for each nutrient (Q1), those in the highest quartile (Q4) had no indication of increased risk of breast cancer with total fat (ORQ4 to Q1=0.76, 95% CI, 0.23-2.45), saturated fat (ORQ4 to Q1=1.43, 95% CI, 0.51-3.98), monounsaturated fat (ORQ4 to Q1=0.96, 95% CI, 0.34-1.72), polyunsaturated fat (ORQ4 to Q1=0.64, 95% CI, 0.23-1.73), n-3 polyunsaturated fat (ORQ4 to Q1=1.10, 95% CI, 0.49-2.48), ALA (ORQ4 to Q1=1.20, 95% CI, 0.51-2.84), EPA (ORQ4 to Q1=1.18, 95% CI, 0.54-2.60), DHA (ORQ4 to Q1=0.66, 95% CI, 0.29-1.51), n-6 polyunsaturated fat (ORQ4 to Q1=0.67, 95% CI, 0.24-1.84) and energy intake (ORQ4 to Q1=1.52, 95% CI, 0.68-3.38). This analysis also showed no linear trend for increased risk of premenopausal breast cancer with increased intake of total fat, fat subtypes and energy (p-trend>0.05).

Multivariate odds ratio analysis for postmenopausal breast cancer risk among 166 cases matched to 166 controls is shown in Table 5. Compared with postmenopausal women in the lowest quartile of intake for each nutrient (Q1), those in the highest quartile (Q4) had no indication of increased risk of breast cancer with total fat (OR=1.36, 95% CI, 0.30-3.12), saturated fat (ORQ4 to Q1=1.75, 95% CI, 0.62-3.40), monounsaturated fat (ORQ4 to Q1=1.74, 95% CI, 0.22-2.79), polyunsaturated fat (ORQ4 to Q1=0.74, 95% CI, 0.39-1.81), n-3 polyunsaturated fat (ORQ4 to Q1=0.78, 95% CI, 0.28-2.18), ALA (ORQ4 to Q1=0.44, 95% CI, 0.14-1.38), EPA (ORQ4 to Q1=1.19, 95% CI, 0.41-

**Table 4. Multivariate Odds Ratios (95% CIs) for Premenopausal Breast Cancer Risk in Relation to Total Fat and Fat Subtype Intake**

	Quartiles of intake				p trend value
	Q1	Q2	Q3	Q4	
Energy					
Cases/ Controls	41/46	42/49	69/59	64/62	
OR <sup>a</sup> (95% CI)	1.00	0.93 (0.42 – 2.08)	1.53 (0.75 – 3.13)	1.27 (0.62 – 2.60)	0.553
OR <sup>b</sup> (95% CI)	1.00	0.98 (0.40 – 2.45)	1.70 (0.76 – 3.08)	1.52 (0.68 – 3.38)	0.150
Total fat					
Cases/ Controls	44/48	44/50	60/50	68/68	
OR <sup>a</sup> (95% CI)	1.00	0.94 (0.43 – 2.03)	1.53 (0.74 – 3.17)	1.20 (0.61 – 2.38)	0.396
OR <sup>b</sup> (95% CI)	1.00	0.69 (0.27 – 1.79)	1.19 (0.42 – 3.38)	0.76 (0.23 – 2.45)	0.753
Saturated fat					
Cases/ Controls	38/49	55/47	52/50	71/70	
OR <sup>a</sup> (95% CI)	1.00	1.07 (0.95 – 2.49)	1.70 (0.79 – 3.68)	1.61 (0.80 – 3.26)	0.713
OR <sup>b</sup> (95% CI)	1.00	1.00 (0.84 – 2.78)	1.61 (0.62 – 3.20)	1.43 (0.51 – 3.98)	0.629
Monounsaturated fat					
Cases/ Controls	47/47	43/51	59/51	67/67	
OR <sup>a</sup> (95% CI)	1.00	0.74 (0.34 – 1.58)	1.25 (0.61 – 2.54)	0.98 (0.50 – 1.92)	0.975
OR <sup>b</sup> (95% CI)	1.00	0.86 (0.36 – 2.02)	1.26 (0.50 – 3.14)	0.96 (0.34 – 1.72)	0.911
Polyunsaturated fat					
Cases/ Controls	51/49	43/54	66/57	56/56	
OR <sup>a</sup> (95% CI)	1.00	0.63 (0.30 – 1.31)	1.15 (0.59 – 2.24)	0.93 (0.46 – 1.84)	0.998
OR <sup>b</sup> (95% CI)	1.00	0.58 (0.24 – 1.36)	0.86 (0.36 – 2.03)	0.64 (0.23 – 1.73)	0.609
n-3 polyunsaturated fat					
Cases/ Controls	52/57	49/46	64/55	51/58	
OR <sup>a</sup> (95% CI)	1.00	1.29 (0.63 – 2.62)	1.45 (0.75 – 2.77)	0.94 (0.48 – 1.84)	0.728
OR <sup>b</sup> (95% CI)	1.00	1.30 (0.56 – 2.98)	1.67 (0.77 – 3.59)	1.10 (0.49 – 2.48)	0.637
Alpha linolenic acid (ALA)					
Cases/ Controls	47/57	57/50	57/54	55/55	
OR <sup>a</sup> (95% CI)	1.00	1.68 (0.84 – 3.36)	1.48 (0.75 – 2.93)	1.36 (0.69 – 2.70)	0.751
OR <sup>b</sup> (95% CI)	1.00	1.41 (0.65 – 3.05)	1.02 (0.44 – 2.32)	1.20 (0.51 – 2.84)	0.807
Eicosapentanoic acid (EPA)					
Cases/ Controls	53/55	53/47	66/54	50/54	
OR <sup>a</sup> (95% CI)	1.00	0.87 (0.43 – 1.74)	1.43 (0.74 – 2.74)	0.93 (0.47 – 1.85)	0.968
OR <sup>b</sup> (95% CI)	1.00	0.92 (0.41 – 2.05)	1.42 (0.67 – 3.00)	1.18 (0.54 – 2.60)	0.410
Docosahexanoic acid (DHA)					
Cases/ Controls	52/53	60/58	61/50	43/55	
OR <sup>a</sup> (95% CI)	1.00	1.08 (0.55 – 2.09)	1.40 (0.71 – 2.77)	0.68 (0.33 – 1.39)	0.314
OR <sup>b</sup> (95% CI)	1.00	0.91 (0.43 – 1.96)	1.28 (0.59 – 2.78)	0.66 (0.29 – 1.51)	0.609
n-6 polyunsaturated fat					
Cases/ Controls	52/46	43/56	59/58	62/56	
OR <sup>a</sup> (95% CI)	1.00	0.51 (0.24 – 1.08)	0.82 (0.41 – 1.64)	0.94 (0.47 – 1.86)	0.995
OR <sup>b</sup> (95% CI)	1.00	0.49 (0.20 – 1.17)	0.53 (0.22 – 1.30)	0.67 (0.24 – 1.84)	0.582

ALA, Alpha-linolenic acid; EPA, Eicosapentaenoic acid; DHA, Docosahexaenoic acid; OR, Odds Ratio; CI, Confidence Interval; Logistic regression analysis, Method, Enter; Contrast, Simple; <sup>a</sup>Adjusted for age (continuous); <sup>b</sup>Adjusted for age (continuous), ethnicity, marital status, education, working status, household income, age of menarche, pregnancy history, age at first childbirth, number of live birth, history of breastfeeding, duration of breastfeeding, history of oral contraceptive usage, smoking habits, alcohol consumption, physical activity level, family history of breast cancer, body mass index (BMI) and energy intake; \*Significant trend (Linear regression analysis, p-trend value <0.05)

3.49), DHA (ORQ4 to Q1=1.10, 95% CI, 0.39-3.10), n-6 polyunsaturated fat (ORQ4 to Q1=0.71, 95% CI, 0.29-1.04) and energy intake (ORQ4 to Q1=2.21, 95% CI, 0.93-3.36). This analysis also showed no linear trend for increased risk of postmenopausal breast cancer with increased intake of total fat, fat subtypes and energy (p-trend>0.05).

## Discussion

Association between fat intake and breast cancer

has been extensively debated (Gerber, 2009). Due to inconsistent study findings, various methods of statistical techniques and the latest suggestion that larger body fat composition might be probably protective to premenopausal women but harmful for postmenopausal women towards breast cancer risk. In the current case-control study, no clear association was detected between total fat and fatty acid intake and breast cancer risk among pre- and postmenopausal women. Our findings are consistent with several benchmark reports including meta-analysis studies (Howe et al., 1990; Hunter et al.,

**Table 5. Multivariate Odds Ratios (95% CIs) for Postmenopausal Breast Cancer Risk in Relation to Total Fat and Fat Subtype Intake**

	Quartiles of intake				p trend value
	Q1	Q2	Q3	Q4	
<b>Energy</b>					
Cases/ Controls	28/49	41/47	53/37	44/33	
OR <sup>a</sup> (95% CI)	1.00	1.42 (0.90 – 3.05)	1.70 (0.91 – 3.09)	2.37 (0.96 – 3.95)	0.302
OR <sup>b</sup> (95% CI)	1.00	1.18 (1.01 – 3.95)	1.66 (0.81 – 3.62)	2.21 (0.93 – 3.36)	0.101
<b>Total fat</b>					
Cases/ Controls	35/47	46/46	45/46	40/27	
OR <sup>a</sup> (95% CI)	1.00	1.71 (0.77 – 3.79)	1.65 (0.74 – 3.67)	2.18 (1.56 – 3.19)	0.120
OR <sup>b</sup> (95% CI)	1.00	1.01 (0.37 – 2.75)	0.67 (0.21 – 2.10)	1.36 (0.30 – 3.12)	0.412
<b>Saturated fat</b>					
Cases/ Controls	36/47	52/48	39/46	39/25	
OR <sup>a</sup> (95% CI)	1.00	1.83 (0.85 – 3.94)	1.11 (0.53 – 2.75)	1.85 (0.71 – 3.76)	0.125
OR <sup>b</sup> (95% CI)	1.00	1.12 (0.41 – 3.04)	0.82 (0.37 – 2.19)	1.75 (0.62 – 3.40)	0.436
<b>Monounsaturated fat</b>					
Cases/ Controls	34/48	49/45	43/45	40/28	
OR <sup>a</sup> (95% CI)	1.00	1.15 (0.97 – 2.77)	1.74 (0.77 – 2.92)	2.14 (0.57 – 2.89)	0.115
OR <sup>b</sup> (95% CI)	1.00	1.20 (0.43 – 2.36)	1.87 (0.54 – 2.73)	1.74 (0.22 – 2.79)	0.332
<b>Polyunsaturated fat</b>					
Cases/ Controls	37/46	37/43	55/38	37/39	
OR <sup>a</sup> (95% CI)	1.00	1.11 (0.48 – 2.57)	2.27 (1.23 – 3.05)	1.32 (0.56 – 3.11)	0.135
OR <sup>b</sup> (95% CI)	1.00	0.78 (0.27 – 2.27)	1.68 (0.42 – 2.83)	0.74 (0.39 – 1.81)	0.067
<b>n-3 polyunsaturated fat</b>					
Cases/ Controls	48/45	40/44	36/40	42/37	
OR <sup>a</sup> (95% CI)	1.00	0.76 (0.35 – 1.64)	0.73 (0.32 – 1.65)	1.13 (0.51 – 2.51)	0.779
OR <sup>b</sup> (95% CI)	1.00	0.51 (0.19 – 1.36)	0.67 (0.24 – 1.84)	0.78 (0.28 – 2.18)	0.363
<b>Alpha linolenic acid (ALA)</b>					
Cases/ Controls	41/42	45/45	39/40	41/39	
OR <sup>a</sup> (95% CI)	1.00	1.04 (0.47 – 2.28)	0.99 (0.43 – 2.27)	1.14 (0.50 – 2.60)	0.727
OR <sup>b</sup> (95% CI)	1.00	1.03 (0.38 – 2.76)	0.57 (0.20 – 1.65)	0.44 (0.14 – 1.38)	0.063
<b>Eicosapentanoic acid (EPA)</b>					
Cases/ Controls	45/46	39/42	47/44	35/34	
OR <sup>a</sup> (95% CI)	1.00	0.90 (0.41 – 1.99)	1.15 (0.54 – 2.44)	1.09 (0.46 – 2.60)	0.626
OR <sup>b</sup> (95% CI)	1.00	0.57 (0.21 – 1.55)	0.80 (0.30 – 2.16)	1.19 (0.41 – 3.49)	0.777
<b>Docosahexaenoic acid (DHA)</b>					
Cases/ Controls	43/43	42/41	42/45	39/37	
OR <sup>a</sup> (95% CI)	1.00	1.04 (0.47 – 2.31)	0.88 (0.40 – 1.94)	1.10 (0.48 – 2.53)	0.864
OR <sup>b</sup> (95% CI)	1.00	0.76 (0.28 – 2.04)	0.82 (0.30 – 2.25)	1.10 (0.39 – 3.10)	0.697
<b>n-6 polyunsaturated fat</b>					
Cases/ Controls	41/49	32/41	56/37	37/39	
OR <sup>a</sup> (95% CI)	1.00	0.81 (0.34 – 1.92)	2.69 (1.24 – 5.82)	1.21 (0.53 – 2.76)	0.126
OR <sup>b</sup> (95% CI)	1.00	0.57 (0.19 – 1.64)	1.27 (0.43 – 3.69)	0.71 (0.29 – 1.04)	0.068

ALA, Alpha-linolenic acid; EPA, Eicosapentaenoic acid; DHA, Docosahexaenoic acid; OR, Odds Ratio; CI, Confidence Interval; Logistic regression analysis, Method, Enter; Contrast, Simple; <sup>a</sup>Adjusted for age (continuous); <sup>b</sup>Adjusted for age (continuous), ethnicity, marital status, education, working status, household income, age of menarche, pregnancy history, age at first childbirth, number of live birth, history of breastfeeding, duration of breastfeeding, history of oral contraceptive usage, smoking habits, alcohol consumption, physical activity level, family history of breast cancer, body mass index (BMI) and energy intake; \*Significant trend (Linear regression analysis, p-trend value <0.05)

1996; Smith-Warner et al., 2001) and findings from the Nurses' Health Study (Holmes et al., 1999; Byrne et al., 2002; Kim et al., 2006).

Positive association was found for total fat intake among premenopausal women in the Nurses' Health Study II (Cho et al., 2003). Women in the highest quartile of fat intake (up to 38% of energy intake) had a slight increased risk for breast cancer (RR=1.25, p-trend=0.06). A combined analysis of 12 case-control studies found no significant effect of increased risk of pre- and postmenopausal breast cancer with total fat

intake up to 100 g/day (Howe et al., 1990). The Nurses' Health Study found that increment of 5% total fat per energy intake showed no significant effect towards risk of pre- and postmenopausal breast cancer (Holmes et al., 1999). Studies in Germany and Sweden also found no significant effect of increased risk of pre- and postmenopausal breast cancer with total fat intake up to 80 g/day (Hermann et al., 2002; Lof et al., 2007). The Breast Cancer Detection Demonstration Project (BCDDP) follow-up cohort study found no significant effect of increased risk of postmenopausal breast cancer

with total fat intake up to 45% of energy intake (Velie et al., 2000). In the same study, when analysis was confined to postmenopausal women with no history of benign breast disease, there was a significant increased risk of breast cancer with an RR of 2.20 ( $p$ -trend $<0.001$ ). This was not supported by findings from the Nurses' Health Study, which also analyzed postmenopausal women with no history of benign breast disease (Byrne et al., 2002). They found no increase in rate of breast cancer among postmenopausal women even with a greater intake of total fat. A positive association was found between total fat intake and postmenopausal breast cancer risk in the NIH-AARP Diet and Health Study (Thiebaut et al., 2007). The hazard ratio (HR) of breast cancer for the highest (median intake, 40.1% energy from total fat) versus the lowest (median intake, 20.3% energy from total fat) quartile of total fat intake was 1.11 (95% CI = 1.00 to 1.24;  $p$ -trend=0.017) suggesting an increased risk with higher intake of total fat. Voorrips et al. (2002) from the Netherlands Cohort Study did not find any significant effect of increased risk for postmenopausal breast cancer with total fat intake up to 86 g/day. Total fat intake during midlife did not affect the risk of postmenopausal breast cancer as confirmed by Nurses' Health Study findings (Kim et al. 2006). Prentice et al. (2006) through the Women's Health Initiative randomized controlled dietary modification trial, intervened postmenopausal women with a low-fat (20% of energy) dietary pattern after a follow up period of 8.1 years and found no statistically significant reduction in invasive breast cancer although there was a trend of decreasing risk. Wynder et al. (1997) hypothesized that a threshold effect may exist for dietary fat which makes it difficult to detect an association between fat intake and breast cancer risk in Western populations where few people consume a diet containing 20% or less of energy contributed from total fat. A case-control study among a group with a low fat diet in Indonesia found that 40 g/day of total fat intake might be an important determinant of pre- and postmenopausal breast cancer risk compared to those consuming 26 g/day of total fat with a two-fold increase in risk (Wakai et al., 2000).

Evidence from studies done without stratification according to menopausal status was useful for judgment of breast cancer risk due to their higher statistical power and data availability. Boyd et al. (2003) from a meta-analysis from 45 case-control and cohort studies concluded that higher intake of total fat intake increases the risk for breast cancer with a cumulative increase about 13%. In a population based case-control study in the San Francisco Bay area, Wang et al. (2008) found a significant increased risk of breast cancer with an OR of 1.35 ( $p$ -trend $<0.01$ ) when intake of total fat was higher compared to lower intakes. The EPIC cohort, from their recent report showed that no association between high fat intake and overall breast cancer risk was found with HR of 1.02 (95% CI: 0.90, 1.17;  $p$ -trend =0.601) for

the highest quartile (113.4 g/day) of total fat intake compared with the lowest quartile (Sieri et al., 2008). In the Asia Pacific region, studies done in Japan and Singapore did not find any association between total fat intake and overall breast cancer risk (Kuriki et al., 2007; Gago-Dominguez et al., 2003). However, a local study in Malaysia found that women with a high fat diet ( $>65$ g/day) were at elevated risk compared to those consuming a low fat diet with an OR of 3.84 (Kamarudin et al., 2006). The researchers agreed with findings by Wakai et al. (2000) although Malaysian total fat intake is somewhat higher than in Indonesia.

There is an interest in the varying role that different types of fat might have on breast cancer risk. The deleterious effect of saturated fat on premenopausal breast cancer risk was not evident in the current study and concurs with various studies done previously (Holmes et al. 1999; Hermann et al. 2002; Lof et al. 2007). In contrast, Cho et al. (2003) found that, relative to the premenopausal women in the lowest quartile of saturated fatty acid intake, women in the highest intake (14% of energy intake) were related to modestly elevated breast cancer risk (RR=1.12,  $p$ -trend=0.02). A similar negative trend was observed for the relationship between saturated fat intake and postmenopausal breast cancer risk in the current study, which is also consistent with previous studies (Holmes et al. 1999; Velie et al. 2000; Byrne et al. 2002; Voorrips et al. 2002; Kim et al. 2006; Lof et al. 2007). They failed to prove the significant effect of increased risk for postmenopausal breast cancer in relation to saturated fat intake. Interestingly, only the NIH-AARP Diet and Health Study found a significant increased risk of postmenopausal breast cancer with a higher intake of saturated fat (Thiebaut et al., 2007). The HR of breast cancer for the highest (median intake, 13.2% energy from saturated fat) versus the lowest (median intake, 5.8% energy from saturated fat) quartile of total fat intake was 1.18 (95% CI = 1.06 to 1.31;  $p$ -trend=0.004). Boyd et al. (2003) using a meta-analysis design produced similar results indicating a 19% increase on overall breast cancer risk with a higher intake of saturated fat (RR=1.19). The EPIC cohort findings were coherent with previous meta-analysis which shows an association between high saturated fat intake and greater overall breast cancer risk with HR of 1.13 (95% CI: 1.00, 1.27;  $p$ -for trend=0.038) for the highest quartile (45 g/day) of saturated fat intake compared with the lowest quartile (Sieri et al., 2008). Other studies conducted in Western countries (Goodstine et al., 2003; Nkondjock et al., 2003; Wang et al., 2008) including studies done in Japan (Kuriki et al., 2007) and Singapore (Gago-Dominguez et al., 2003) failed to show a significant increased risk of overall breast cancer with saturated fat intake ( $p>0.05$ ). Alternatively, pooled analysis of eight cohort studies suggests a weak positive association with substitution of saturated fat for carbohydrate consumption for an increment of 5% of energy with a RR of 1.09 (95%

CI: 1.00 –1.19) (Smith-Warner et al., 2001). It is noteworthy that the sources and variation of saturated fat from diet are different between Western and Asian countries. Among Asians, palm oil and coconut milk are the major sources for saturated fat with varied intake levels, while animal fat and dairy products were main sources for Western population with a limited intake levels. However, this scenario is changing with the adoption of Western eating habits by Asians owing to increase socioeconomic status.

In this study, a high intake of monounsaturated fat shows a lack of protective effects towards pre- and postmenopausal breast cancer. The Nurses' Health Study and Swedish Women's Lifestyle and Health cohort found a similar pattern of no effects for premenopausal breast cancer risk but significant decreased risk for postmenopausal breast cancer with high intake of monounsaturated fat (Holmes et al., 1999; Lof et al., 2007). Among premenopausal women, a study in Germany found no association between breast cancer risk and intakes of monounsaturated fat (Hermann et al., 2002). Cho et al. (2003) disagrees and shows that relative to the premenopausal women in the lowest quartile of monounsaturated fat intake, women in the highest intake (15% of energy intake) were related to modestly elevated breast cancer risk (RR=1.10, p-trend=0.87). Consistent with Holmes et al. (1999) and Lof et al. (2007), the Netherlands cohort study found a significant effect of decreased risk by 39% for postmenopausal breast cancer with monounsaturated fat intake up to 27 g/day (RR=0.61, p-trend=0.001) (Voorrips et al., 2002). Studies in America found significant increased risk of postmenopausal breast cancer with higher intake of monounsaturated fat from their diet (Velie et al., 2000; Thiebaut et al., 2007; Wang et al., 2008). Further analysis on the Nurses' Health Study cohort restricted to postmenopausal women without a history of benign breast disease found that the protective effects of oleic acid, a prominent monounsaturated fatty acid in diet, no longer exists (Byrne et al., 2002). There was also no association between midlife intake of monounsaturated fat and the risk of postmenopausal breast cancer (Kim et al., 2006). A case-control study in Canary Islands, Spain found a significant inverse relationship between monounsaturated fat intake and overall breast cancer risk (Garcia-Segovia et al., 2006). Compared to the first quartile of intake, the highest quartile of monounsaturated fat intake was significantly related to a lower risk of breast cancer (OR=0.52; 95% CI 0.30-0.92). Nevertheless, no association was found between monounsaturated fat intake and overall breast cancer risk in the meta-analysis report (Boyd et al., 2003), EPIC cohort study (Sieri et al., 2008), French-Canadian and American cohorts (Nkondjock et al., 2003; Goodstine et al., 2003) and Asian cohorts (Gago-Dominguez et al., 2003; Kuriki et al., 2007). As we can observe, the relationship between monounsaturated fat intake and breast cancer risk varies between different

parts of the world suggesting difference in food sources. Olive oil is the major source of monounsaturated fat in Mediterranean countries. For Westerners the main sources of monounsaturated fat are margarine and red meat while Asians consume a more varied range, which includes palm oil, beans, legumes and red meat.

Studies in animal models and observation in humans provided evidence that a high intake of n-6 polyunsaturated fat stimulates several stages in the development of breast cancer, from an increase in oxidative damage to effects on cell proliferation, free oestrogen levels and hormonal catabolism (Bartsch et al. 1999). In contrast, marine fish-derived n-3 polyunsaturated fat seems to prevent breast cancer by influencing the activity of enzymes and proteins related to intracellular signaling and, ultimately, cell proliferation. However, most epidemiological studies did not find any effect of total polyunsaturated fat intake on pre-, postmenopausal or overall breast cancer risk and the evidence is consistent with the findings of the current study (Holmes et al., 1999; Velie et al., 2000; Byrne et al., 2002; Hermann et al., 2002; Voorrips et al., 2002; Cho et al., 2003; Boyd et al., 2003; Gago-Dominguez et al., 2003; Goodstine et al., 2003; Nkondjock et al., 2003; Kim et al., 2006; Kuriki et al., 2007; Lof et al., 2007; Sieri et al., 2008; Wang et al., 2008). Contrastingly, the NIH-AARP Diet and Health Study cohort found an increased risk for postmenopausal breast cancer with higher intake of total polyunsaturated fat intake (Thiebaut et al., 2007). The HR of postmenopausal breast cancer for the highest (median intake, 10.3% energy from polyunsaturated fat) versus the lowest (median intake, 4.5% energy from polyunsaturated fat) quartile of polyunsaturated fat intake was 1.12 (95% CI=1.01 to 1.25; p-trend=0.022). When looking into n-3 polyunsaturated fat, Kim et al. (2009) found a significant reduction in pre- and postmenopausal breast cancer risk, but the relationship is stronger among Korean premenopausal women with intake more than 0.3 g/day (OR=0.46, 95% CI: 0.22-0.96, p-trend=0.040). In the same study, EPA and DHA, which are marine sources of n-3 polyunsaturated fat, were observed to have protective effect on postmenopausal but not premenopausal breast cancer risk. Women who consumed more than 0.10 g/day of EPA were at 62% lower in risk (OR=0.38, 95% CI: 0.15-0.96) while those consuming DHA of more than 0.21 g/day were 68% lower in risk (OR=0.32, 95% CI: 0.13-0.82) compared to those in the lowest quartile of intake. These findings were comparable to other studies in Asia Pacific region, which found n-3 polyunsaturated fat from marine sources, referred to as n-3 highly unsaturated fat were related to significant decrease in risk of breast cancer (Gago-Dominguez et al., 2003; Kuriki et al., 2007). In the E3N-EPIC Cohort study in France, breast cancer risk was inversely associated with ALA intake from fruit and vegetables (HR=0.74, 95% CI: 0.63-0.88, p-trend<0.01), and from vegetable

oils (HR=0.83, 95% CI: 0.71-0.97, p-trend=0.017) (Thiebaut et al., 2009). Breast cancer risk was positively related to ALA intake from nut mixes (p-trend=0.004) and processed foods (p-trend=0.068), as was total ALA intake among women in the highest quartile of dietary vitamin E (p-trend=0.036). Other studies from the European and American cohort failed to find any association between specific n-3 polyunsaturated fat intake and breast cancer (Holmes et al., 1999; Voorrips et al., 2002; Cho et al., 2003; Goodstine et al., 2003; Nkondjock et al., 2003; Kim et al., 2006). A systematic review on n-3 polyunsaturated fat intake and breast cancer risk found no strong evidence to suggest significant protective effect (MacLean et al., 2006). As for n-6 polyunsaturated fat, there was no association evident in studies which evaluated the relationship with breast cancer (Gago-Dominguez et al., 2003; Nkondjock et al., 2003; Thiebaut et al., 2009). In the study reported by Thiebaut et al. (2009), linoleic acid intake, an abundant n-6 polyunsaturated fat in diet, from vegetable oils showed a decreased risk of borderline significance (HR=0.86, CI: 0.74 – 1.00, p-trend=0.042), whereas linoleic acid from processed food was associated with an increased risk (HR=1.18, CI: 1.01 – 1.38, p-trend=0.080). Meta-analysis from 30 case-control and cohort studies also failed to show significant association between linoleic acid intake and breast cancer risks (Zock & Katan, 1998). In the current study, no relationships were observed between pre- or postmenopausal breast cancer risk and specific n-3 and n-6 polyunsaturated fat intakes.

The results of this study must be interpreted in the light of possible biases that case-control studies are subject to. A major limitation is the recall biases of exposure among cases who might over-report foods that they believe may have contributed to their diagnosis, and under-report healthier foods that they believe may have prevented their disease (Morton et al., 2006). In addition, controls who participate may be more health-conscious and perhaps consume healthier diet than those who refused to take part in the study. 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. 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. Measurement error in reported dietary intake from FFQ, which remains one of the major problems in nutritional epidemiology, could have affected our results due to misclassification of fat intake. A study found a null association with total fat intake using FFQ data but a positive association when a 7-day food diary was used which indicates a positive finding may therefore depend on the dietary method used (Bingham et al. 2003). FFQ remains a

reliable method and the results are generally accepted as estimates and indicative of dietary patterns when investigating relationship between fat intake and breast cancer risk. Nevertheless, a high co-linearity for total fat and fat subtypes might exist and conceals the main effect in the current study. We therefore tried to separate the effects of total fat and each fat subtypes, but failed to observe changes on results. A wide range of potentially confounding variables i.e. established risk factors for breast cancer, BMI and physical activity were included in the adjusted model of risk as well, but it does not appreciably alter the estimates of risk. However, the impact of fat and fat subtype intake during premenopausal years on postmenopausal breast cancer risk is still unknown due to the nature of dietary intake data collection in this study, which used single data from FFQ using a one-year reference method. The strength of this study was adequate sample of cases and controls stratified for menopausal status to provide sufficient data for statistical analysis. This study was able to provide simultaneous description and analysis of several established risk factors for breast cancer as well as nutrient intakes specifically total fat and fat subtypes. The FFQ and database of nutrients used which was specially designed for the local population in this study made it possible to produce reliable and valid data for analysis. Dose-response relations over different levels of intakes were examined in all analyses using continuous data. Restriction of cases with histopathology examination reports which confirms the status of disease further strengthened this study.

In conclusion, the association between a greater intake of total fat or saturated fat and increased risk of breast cancer among pre- and postmenopausal women within the Malaysian population was not observed in this study. The protective effects of monounsaturated and polyunsaturated fat specifically n-3 polyunsaturated fat were also not seen in the current study. A possible explanation for differences in findings in this study compared to the whole body of evidence based on studies done in the West might be due to difference sources of food intake and quality of fat used among Asian population and specifically the among current study cohort in Malaysia. Further evaluation using food intake data classified into food groups from the current cohort will be of interest to support these study findings. Intake of total fat and fat subtypes should always be in line with recommendation of local dietary guidelines to prevent other non-communicable diseases.

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