RESEARCH ARTICLE

Dietary Carbohydrate, Fiber and Sugar and Risk of Breast Cancer According to Menopausal Status in Malaysia

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Abstract

Background: Dietary carbohydrate, fiber and sugar 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. Objective: To examine the association of premenopausal and postmenopausal breast cancer risk with dietary carbohydrate, fiber and sugar intake. Materials and Methods: This population based case-control study was conducted in Malaysia with 382 breast cancer patients and 382 controls. Food intake pattern 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. Results: A significant two fold increased risk of breast cancer among premenopausal (OR Q_4 to Q_1=1.93, 95%CI: 1.53-2.61, p-trend=0.001) and postmenopausal (OR Q_4 to Q_1=1.87, 95%CI: 1.03-2.61, p-trend=0.045) women was observed in the highest quartile of sugar. A higher intake of dietary fiber was associated with a significantly lower breast cancer risk among both premenopausal (ORQ_4 to Q_1=0.31, 95%CI: 0.12-0.79, p-trend=0.009) and postmenopausal (ORQ_4 to Q_1=0.23, 95%CI: 0.07-0.76, p-trend=0.031) women. Conclusions: Sugar and dietary fiber intake were independently related to pre- and postmenopausal breast cancer risk. However, no association was observed for dietary carbohydrate intake.

Keywords: carbohydrate - fiber - sugar - premenopausal - postmenopausal - breast cancer

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Introduction

Breast cancer incidence in Malaysia, a developing Asian country, is at an Age-Standardized Rate (ASR) of 29.1 per 100,000 populations in year 2007 (Zainal Ariffin and Nor Saleha 2011). 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 (Ferlay et al., 2010). Nutrition transition in terms of increased energy intake, animal fat, red meats, complex, simple carbohydrate and decreased intake of plant foods, a major source of dietary fiber has been observed during the last several decades in Asia. Concurrently, there have been striking changes in mortality rates of breast cancer among other cancers which lagged around 10 years from the beginning of the nutrition transition towards a westernized diet in selected geographical location in East Asia (Zhang et al., 2012). In the past decade, dietary carbohydrate, fiber and sugar has gained much attention in relation towards breast cancer risk according to menopausal status, but studies have been limited in developed countries (Cho et al., 2003; Holmes et al., 2004; Romieu et al., 2004; Mattisson et al., 2004; Nielsen et al., 2005; Giles et al., 2006; Cade et al., 2007; Lajous et al., 2008; Suzuki et al., 2008; Larsson et al., 2009; Wen et al., 2009; Park et al., 2009; Shikany et al., 2011; Zaineddin et al., 2012; Ferrari et al., 2013; Li et al., 2013; Woo et al., 2013). A few studies have appeared from South-East Asia and Eastern Europe (Kruk and Marchlewicz, 2013; Sangrajrang et al., 2013). Rice, bread, noodles, traditional snacks (kuih), tubers, various tropical fruits and green leafy vegetables are rich sources of dietary carbohydrate, fiber, sugar and have been the staple diet among Asian population specifically in Malaysia. Therefore, we investigated associations between dietary carbohydrates, fiber and sugar intake and risk of breast cancer in a retrospective study of premenopausal and postmenopausal women with a wide range of relevant exposures.

Materials and Methods

Study population

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

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Lumpur, Malaysia as part of Genetics, Molecular and Proteomic Study of Primary Breast Cancer in Malaysia among women aged 21 to 79 (Sulaiman et al., 2011). 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 (Shahril et al., 2008; Sulaiman et al., 2011). 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, carbohydrate, sugar and dietary fiber were computed using Malaysian food composition table (Tee et al., 1997) and supported by current US Department of Agriculture food composition sources (U.S. Department of Agriculture Agricultural Research Service 2006). 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 dietary carbohydrate, fiber, sugar 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) and energy (kcal) intake. All statistical analysis was done using Statistical Package for Social Sciences (SPSS) for Windows version 20.0 (SPSS Inc., Chicago, Illinois, USA).

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 subjects by case and control group. The mean age of the subjects 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,

Table 1. Selected Characteristics of the Study Subjects

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	(3146.0)	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

Table 2. Multivariate OR for the Association between Dietary Carbohydrate, Sugar and Fiber, and Breast Cancer Risk According to Menopausal Status

		Quartiles of intake				p trend
		1	2	3	4	
Premenopausal						
Carbohydrate	Case/Control	39/54	56/54	57/54	64/54	
	OR[a] (95%CI)	1.00	1.45 (0.73-3.14)	1.46 (0.68-3.03)	1.63 (0.76-3.26)	0.540
	OR[b] (95%CI)	1.00	1.52 (0.62-3.75)	1.13 (0.41-3.13)	1.21 (0.36-4.09)	0.928
Sugar	Case/Control	38/54	43/54	65/54	70/54	
	OR[a] (95%CI)	1.00	1.13 (0.57-2.75)	1.71 (0.99-2.80)	1.84 (1.34-2.79)	0.002*
	OR[b] (95%CI)	1.00	1.20 (0.51-2.83)	1.73 (1.15-3.00)	1.93 (1.53-2.61)	0.001*
Dietary fiber	Case/Control	55/54	81/54	46/54	34/54	
	OR[a] (95%CI)	1.00	1.47 (1.10-2.91)	0.84 (0.53-2.24)	0.62 (0.18-0.87)	0.010*
	OR[b] (95%CI)	1.00	1.73 (0.85-2.52)	0.91 (0.40-2.08)	0.31 (0.12-0.79)	0.009*
Postmenopausal						
Carbohydrate	Case/Control	30/42	43/41	47/41	46/42	
	OR[a](95%CI)	1.00	1.44 (0.78-2.23)	1.57 (0.83-2.85)	1.53 (0.59-2.49)	0.400
	OR[b](95%CI)	1.00	1.57 (0.57-2.11)	1.86 (0.54-2.38)	1.72 (0.46-2.57)	0.668
Sugar	Case/Control	29/42	33/41	51/41	53/42	
	OR[a](95%CI)	1.00	1.14 (0.28-1.94)	1.76 (1.24-2.90)	1.83 (1.04-2.94)	0.004*
	OR[b](95%CI)	1.00	1.29 (0.07-1.24)	1.83 (0.63-2.86)	1.87 (1.03-2.61)	0.045*
Dietary fiber	Case/Control	52/42	40/41	37/41	37/42	
	OR[a](95%CI)	1.00	0.77 (0.29-2.62)	0.71 (0.14-1.51)	0.71 (0.10-1.02)	0.059
	OR[b](95%CI)	1.00	0.91 (0.38-2.71)	0.41 (0.12-1.35)	0.23 (0.07-0.76)	0.031*

*Significant trend (Linear regression analysis, p-trend value <0.05); 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) and energy intake

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.

Multivariate OR for the association between dietary carbohydrate, sugar and fiber, and breast cancer risk according to menopausal status is shown in Table 2. The median and inter-quartile cut off points were 235.5 (212.6, 264.1) g/day for carbohydrate 12.1 (7.7, 17.8) g/day for dietary fiber and 33.6 (21.3, 61.3) g/day for sugar intake. Compared with premenopausal women in the lowest quartile of dietary carbohydrate intake (Q_1), those in the highest quartile (Q_4) had no indication of significant increased risk of breast cancer (ORQ_4 to Q_1=1.21, 95%CI: 0.36-4.09, p-trend=0.928). Similarly, the same trend was observed between dietary carbohydrate intake and postmenopausal breast cancer risk (ORQ_4 to Q_1=1.72, 95%CI: 0.46-2.57, p-trend=0.668). However, an elevated risk of pre- and postmenopausal breast cancer were observed with higher intake of added sugar from foods and beverages. A significant twofold increased risk of breast cancer was observed among premenopausal (ORQ_4 to Q_1=1.93, 95%CI: 1.53-2.61, p-trend=0.001) and postmenopausal (ORQ_4 to Q_1=1.87, 95%CI: 1.03-2.61, p-trend=0.045) women in the highest quartile of sugar intake compared to those in lowest quartile of intake. In contrast, both pre- and postmenopausal women were estimated to have a significantly lower risk of breast cancer with higher intake of dietary fiber compared to lower intake. With an intake of dietary fiber more 17.8 g/day at highest quartile, breast cancer risk reduction effect was up to 69% (ORQ_4 to Q_1=0.31, 95%CI: 0.12-0.79, p-trend=0.009) among premenopausal women and 77% (ORQ_4 to Q_1=0.23, 95%CI: 0.07-0.76, p-trend=0.031) among postmenopausal women in our study.

Discussion

Our study found no significant association between dietary carbohydrate intake with pre- and postmenopausal breast cancer risk. However, higher intake of sugar intake was seen to have significant potential to increase risk while diet high in dietary fiber was protective towards risk of breast cancer among both pre- and postmenopausal women in our study.

Similar finding from the Nurses' Health Study II among premenopausal women was reported with comparable amount of carbohydrate intake at the highest quartile with our study (60% *vs* 57% of energy) (Cho et al., 2003). The relationship between carbohydrate intake and premenopausal breast cancer risk remains insignificant even when intake during adolescence was studied among the same cohort (Linos et al., 2010). This was agreed by another cohort of Nurses' Health Study which found there was no significant association between carbohydrate intake and breast cancer risk among premenopausal women (Holmes et al., 2004). Studies among postmenopausal women were more intensively conducted but majority of them found no significant association between carbohydrate intake and breast cancer risk at an intake of 50% to 55% of energy (Holmes et al., 2004; Nielsen et al., 2005; Lajous et al., 2008; Larsson et al., 2009; Shikany et al., 2011). However, at a higher intake of carbohydrate achieving 82% of energy contribution (344 g/day), a prospective study in China found a significant two-fold increased risk of breast cancer among premenopausal (HR=2:01; 95%CI: 1.26 to 3.19), but not postmenopausal (Wen et al., 2009). Postmenopausal women in Australia also were found to be not affected by risk of breast cancer irrespective of their amount of carbohydrate intake (Giles et al., 2006). Interestingly, a case control study in Mexico found that carbohydrate intake at the highest quintiles with consumption more than 62% of energy, could increase risk of breast cancer significantly among both premenopausal (OR=2.31; 95%CI: 1.36-3.91) and postmenopausal (OR=2.22; 95%CI: 1.49-3.30) women (Romieu et al., 2004). Since only studies with higher carbohydrate consumption among their cohort member showed a positive association, there is a possibility that the connection between carbohydrate and breast cancer risk depends on the amount of carbohydrate intake itself.

In our current study, the highest quartile of sugar intake was more than 61 g per day and this is equal to 14% of energy, which were considered very high. The detrimental effect of high sugar intake in this study was recorded towards risk of pre- and postmenopausal breast cancer by two times or more compared to those in the lowest quartile of intake. This was consistent with findings by Romieu et al. (2004) who reported that sugar intake of more than 8.5% of energy could possibly increase the risk of breast cancer significantly with larger effect on premenopausal (OR=2:51; 95%CI: 1.47-4.26) compared to postmenopausal women (OR=1.84; 95%CI: 1.26-2.71). Nonetheless, many other studies conducted in West failed to establish any association between sugar intake and breast cancer risk according to menopausal status (Nielsen et al., 2005; Giles et al., 2006; Shikany et al., 2011). The lack of agreement between these studies might be due to the difficulty of accurately assessing sugar intake in a complex and variety dietary pattern as in our study. To overcome this problem, the use of a more specific biomarker to prove the earlier hypothesis is warranted (Shikany et al., 2011).

Protective effects of dietary fiber towards breast cancer shown in our study were in line with previous findings among premenopausal (Cade et al., 2007) and postmenopausal women (Mattisson et al., 2004; Park et al., 2009). A significant 69% reduction in premenopausal breast cancer risk and 77% reduction in postmenopausal breast cancer risk were observed with an intake more than 17 g/day of dietary fiber. In the United Kingdom, a developed country, premenopausal women needs more than 30 g/day of dietary fiber to have the same protective effects (RR=0.48; 95%CI: 0.24-0.96) (Cade et al., 2007). However, three other prospective studies found that dietary fiber intake of 25 g per day at the highest quintiles were not able to reduce the risk of premenopausal breast cancer (Cho et al., 2003; Holmes et al., 2004; Ferrari et al., 2013). Much lower intake of dietary fiber at 16 g/day

among premenopausal women in China, was found to have no significant association between dietary fiber intake and breast cancer risk exists (Wen et al., 2009). The same pattern was also observed in a case control study in USA among premenopausal women (Li et al., 2013). Among postmenopausal women, the Malmo Diet and Cancer Cohort found that 25 g/day of dietary fiber can lower breast cancer risk by 42% (IRR=0.58; 95%CI: 0.40-0.84) (Mattisson et al., 2004). Consistently, the NIH-AARP Diet and Health Study found that dietary fiber intake in the highest quintiles can lower postmenopausal breast cancer risk by 13% (RR=0.87; 95%CI: 0.77-0.98) (Park et al., 2009). Although our study findings were supported by two prospective studies, several other studies failed to establish that a diet with low dietary fiber has harmful effects towards breast cancer risk among postmenopausal women (Holmes et al., 2004; Giles et al., 2006; Cade et al., 2007; Suzuki et al., 2008; Wen et al., 2009; Shikany et al., 2011; Zaineddin et al., 2012; Ferrari et al., 2013).

Breast cancer risk among postmenopausal women was found to be increased with obesity since obese women has higher estrogen production from androgen precursor synthesis in adipose tissue (Endogenous Hormones and Breast Cancer Collaborative Group 2011; Basu et al., 2013). Carbohydrate intake and breast cancer risk might be linked due to excessive intake of carbohydrate especially sugar which will cause obesity and increase the levels of endogenous estrogen (van Dam and Seidell 2007). Additionally, when a person is obese, their body insulin level will be higher and this will further develop insulin resistance and increase higher chances of getting breast cancer. A high dietary fiber may reduce the risk of breast cancer by interfering with enterohepatic estrogen circulation and further reduce the amount of breast estrogen (Key et al., 2007). Dietary fiber was also reported to be involved in the mechanism of alteration of gut flora to increase excretion of estrogen as well as act to compete with phytoestrogen to the bind with estrogen (Kumar et al., 2012).

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. 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. Besides, the absence of data on childhood diet might also explain the inconsistencies of findings from various studies since the origin of breast cancer has to be found in childhood in contrast to most other frequent cancers (Mahabir 2013). 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 (Nkondjock and Ghadirian 2007; Park et al., 2009). 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.

In conclusion, only sugar and dietary fiber intake were independently related to pre- and postmenopausal breast cancer risk after controlling for age, other breast cancer risk factors and energy intake. No association was observed for dietary carbohydrate. Our findings provide insight into the Asian diet which is carbohydrate base. 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 glycemic load and glycemic index on their association with breast cancer risk in this region is warranted.

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