RESEARCH COMMUNICATION

Predictors of Breast Cancer among Women in a Northern State of Malaysia: a Matched Case-control Study

Laila Matalqah[1,2]*, Khaldoon Radaideh[3], Zuraidah Mohd Yusoff[1], Ahmed Awaisu[4]

Abstract

Background: Breast cancer has been increased in South East Asia countries, but there are limited data for breast cancer risk factors in these countries. To clarify the risk for breast cancer among the Malaysian women, a matched case-control study was conducted. Method: Between October 2009 and April 2010, a survey was prospectively conducted among women admitted to clinics of Penang General Hospital for examination and/or treatment by using a questionnaire. Therefore, characteristics of patients diagnosed with breast cancer (n = 150) were compared with control cases (n = 150) admitted to hospital for non-neoplastic, non-hormone related diseases. Results: Family history of a distant relative with breast cancer (OR= 2.84), history of first-degree relatives with breast cancer (OR= 2.95), history of benign breast disease (OR= 2.43), menstrual irregularity (OR= 4.24), and use of oral contraceptive pills (OCP) (OR= 2.15) were found to be significant risk factors for breast cancer in our population. Furthermore, education more than 11 years (OR= 0.40), breastfeeding (OR= 0.50), being employed (OR= 0.45) and practicing low fat diet (OR= 0.53) were strongly protective against breast cancer development. Conclusion: The results emphasize the importance of conducting a series of awareness campaigns that highlights the protective role of longer breastfeeding period against breast cancer and the negative relationships between OCP use and high fat diet with this disease.

Keywords: Breast cancer - risk factors - case-control study - Penang, Malaysia

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Introduction

Breast cancer is the most prevalent cancer in the world with estimated survival rates was 57% in the developing countries (Parkin et al. 2005). It is the most common site-specific cancer among Malaysian women regardless of their ethnicity (Lim et al., 2002; Lim and Halimah, 2004). Approximately 1 in 20 Malaysian woman has a lifetime risk of developing this disease (Lim et al., 2002). The trend in breast cancer mortality in Malaysia had increased from 0.6 in 1983 to 1.8 per 100,000 women in 1992. In 2003, the second report of The National Cancer Registry showed that breast cancer comprised 30.4% of all female cancers in Malaysia; there were 3738 female breast cancer cases were reported, out of these cases, 64.1% were in women between 40 and 60 years of age (Lim and Halimah, 2004). Breast cancer incidence and mortality may have alterations in different geographical areas across Malaysia. The distribution of breast cancer incidence varies significantly due to geographical, economic, social, cultural and ethical factors with the highest incidence rate reported in Penang Island (Rosemawati & Sallehudin, 2001).

Numerous epidemiological studies on risk factors of breast cancer have produced evidence on international variations. Many studies in the literature have reported that breast cancer is related to the reproductive life of women; such as early menarche (≤ 12 years old), late menopause (≥ 55 years old), nulliparity, late age at first birth (> 30 years old) (Brinton et al., 1983, 1988; Ewertz et al., 1990) , lifestyle factors such as alcohol consumption (Kropp et al., 2001; Brown et al., 2009), high fat diet consumption (Wakai et al., 2003; Lima et al., 2008) and tobacco smoking (Bennicke et al., 1995, Terry et al., 2002). These studies are limited among women of developing countries to identify the risk factors to conduct new prevention strategies. Hence, there is a need to develop a study oriented toward countries with limited financial resources.

This study is the first to assess breast cancer risk factors among Malaysian women in Penang State; a northern state of Malaysia. Determining the risk factors of breast cancer would help to identify targeted groups who may benefit from screening programs or other preventive measures. This in turn, would offer hopeful promise of modifying those factors, thus preventing breast cancer or even decreasing its incidence.

*[1]Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia (USM), [2]School of Pharmacy, Allianze University College of Medical Science (AUCMS), [3]Department of Medical Physics, School of Physics, Universiti Sains Malaysia, Penang, Malaysia, [4]College of Pharmacy, Qatar University, Doha, Qatar *For correspondence: lmatalqah@yahoo.com*

Materials and Methods

Study design

Between October 2009 and April 2010, we conducted a matched case-control study at General Penang Hospital, Penang Island, Malaysia, using a standardized questionnaire that was designed in two languages (major Malaysian languages); Malay and English. The forward-backward translation method was used in translating the questionnaire into each language to ensure conceptual equivalence.

As Penang Island's residents compromised of three major ethnic groups (Malay, Chinese and Indian) we chose General Penang Hospital, the busiest public hospitals located in Penang Island, and almost all of the outpatients reside in Penang Island. Therefore, one may think that the outpatient population does reflect a general outpatient population in Malaysia.

Sample size was calculated based on a previous finding that 14% of breast cancer women in Malaysia had a family history of breast cancer [CARIF-UM study 2008] and the relative risk (RR) reported for strong family history ranging from 2.5 to 4.5 [Weir et al., 2007]. An institutional ethical committee approval was obtained by Clinical Research Centre (CRC) and Medical Research Ethics Committee (MREC) of Ministry of Health, Malaysia before starting with the study. Written consent was signed by each case and verbal agreement for interview participation was obtained from each control subject. All the personal information collected was considered confidential. In total, three hundred Malaysian women were enrolled in the study: 150 cases of breast cancer matched with age bracket (±5 years), sex and ethnicity to an equal number of controls.

Controls and cases recruitment

Cases were women with confirmed diagnosis of breast cancer regardless of the stage, above 20 years of age, non-pregnant, without any hormonal and psychological problems selected from convenience sample of prevalent breast cancer women attending the Oncology Clinic, Day-Care Chemotherapy Center, and Oncology Ward, all at Penang Hospital. Only one patient among those approached, declined to participate in this study. The control group consisted of 150 women, above 20 years of age, without any malignancies, gynecological (e.g., artificial menopause by hysterectomy), pregnancy, hormonal, endocrine, and psychological (dementia or schizophrenia) problems selected from the waiting area of different clinics by convenience sampling. Away of all controls interviewed, 3 women (had a history of cancer) and 6 women (with a history of hysterectomy) were excluded. All interviews were conducted at the hospital. Data were collected by a face to face interview by the researcher using a questionnaire form after having the informed consents signed by the participants.

Data collection

A standardized questionnaire consisted of 28 questions related to socio-demographic characteristics of women (age, education, ethnicity, employment status, marital status, monthly income and age at diagnosis), reproductive factors (age at first menstruation, number of children, number of abortions, menopause state and age of menopause, regularity of menstrual cycle, breastfeeding period, and age at first full-term pregnancy), as well as lifestyle and external factors (Use hormone replacement therapy (HRT), oral contraceptive pills (OCP), Smoking, alcohol intake, and practicing low-fat diet, body mass index (BMI), and family history of breast cancer and other types of cancers. Each risk factor for breast cancer and its associated response choices in the questionnaire have specific definitions in the current study

Statistical analysis

All data entry and analyses were conducted using SPSS, version 15, (SPSS, Inc., Chicago, IL). The body mass index was calculated as weight (kg)/height^2 (m^2). Descriptive statistics including mean and standard deviation (SD) were used for continuous variables, whereas frequencies and percentages were used for categorical variables in describing the study population. Chi-square ($\chi 2$) and independent t-tests were used to compare cases and controls for categorical and continuous variables, respectively. Univariate logistic regression model was used in the statistical analyses to evaluate the significant factors associated with breast cancer risk and examine the association between breast cancer status and various independent risk factors by estimating the crude odds ratio (OR) and 95% confidence intervals (CI).

Only factors with univariate significance level of less than 0.20 (Dales & URY, 1978; Greenland, 2003) were included in the multivariate forward stepwise conditional logistic regression model to assess multiple risk factors for breast cancer simultaneously. For each factor in the model, the likelihood of breast cancer risk was estimated by the odds ratios and 95% CI. A p value of < 0.05 was considered significant in the statistical analyses.

Results

The demographic characteristics of the study participants; breast cancer cases (n = 150) and control (n =150) demonstrated no significant differences between the mean age ± SD of cases (52.8 ± 11.1 years, range 23-83 years) and that of controls (52.4 ± 11.5 years, range 22-78 years) with P value = 0.76. The average age of the breast cancer cases at diagnosis within whole breast cancer cases was 50.7 ± 11.0 years and specifically were 48.7, 47.3 and 53.2 among Malay, Indian and Chinese cases, respectively.

The results obtained from univariate conditional logistic regression analysis of breast cancer risk in relation to socio-economic factors and family history demonstrated women with family history of first degree relative had cancer (OR 3.03, 95% CI 1.15–7.94) or distant relative with cancer (OR 2.35, 95% CI 0.95–5.85) were more likely to have increased breast cancer risk. In contrast, occupation (OR 0.44, 95% CI 0.27–0.72) and education (with marginal significance (OR 0.49, 95% CI 0.23–1.06) associated with decreased breast cancer risk.

The distribution of participants according to menstrual

Table 1. Univariate Analysis of Breast Cancer Risk Factors

Risk factors	Cases	Controls	Crude OR	a 95% CI
Age at menarche (years)				
≤ 12	48 (32.0)	48 (32.0)	1	Reference
13-16	95 (63.3)	96 (64.0)	0.99	0.61-1.62
> 16	7 (4.7)	6 (4.0)	1.16	0.37-3.72
Parity				
Null	32 (21.3)	22 (14.7)	1.36	0.69 - 2.69
≤3	71 (47.3)	84 (56.0)	0.79	0.47 - 1.33
≥ 4	47 (31.4)	44 (29.3)	1	Reference
Age at first full-term pregnancy (years)				
< 20	13 (10.9)	16 (12.4)	1	Reference
20–24	39 (32.8)	50 (38.8)	0.96	0.41 - 2.23
25–29	48 (40.3)	48 (37.2)	1.23	0.54 - 2.83
≥ 30	19 (16.0)	15 (11.6)	1.56	0.58 – 4.23
Age at menopause (years)*				
< 55	55 (74.3)	73 (89.0)	1	Reference
≥ 55	19 (25.7)	9 (11.0)	2.8	1.18 - 6.67
Menstrual cycle*				
Regular	138 (92.0)	146 (97.3)	1	Reference
Irregular	12 (8.0)	4 (2.7)	3.17	1.00 - 10.08
Number of miscarriage				
Nil	110 (73.3)	110 (73.3)	1	Reference
1-2	34 (22.7)	37 (24.7)	0.92	0.54 - 1.57
≥ 3	6 (4.0)	3 (2.0)	2	0.49 -8.20
Breastfeeding*				
Never	73 (48.7)	53 (35.3)	1.74	1.09 - 2.76
Ever	77 (51.3)	97 (64.7)	1	Reference group
OCP use (in years)				
Never	110 (73.3)	123 (82.0)	1	Reference
< 1 year	6 (4.0)	2 (1.3)	3.36	0.66 - 16.97
1-5 years	21(14.0)	19 (12.7)	1.24	0.66 - 2.42
> 5 years	13 (8.7)	6 (4.0)	2.42	0.89 - 6.60
HRT use (in years)				
Never	142 (94.7)	139 (92.7)	1	Reference
Ever	8 (5.3)	11 (7.3)	1.41	0.55 - 3.60
Premenopausal BMI (kg/m2)				
< 25	47 (61.8)	44 (64.7)	0.88	0.45 - 1.74
≥ 25	29 (38.2)	24 (35.3)	1	Reference
Postmenopausal BMI (kg/m2)				
< 25	39 (52.7)	50 (61.0)	0.71	0.38 - 1.35
≥ 25	35 (47.3)	32 (39.0)	1	Reference
Alcohol consumption				
Ever	0 (0)	7 (4.7)	0	0
Never	150 (100)	143 (95.3)	1	Reference
Tobacco smoking				
Ever	0 (0)	3 (2.0)	0	0
Never	150 (100.0)	147 (98.0)	1	Reference
Practice low fat diet*				
Yes	61 (40.7)	83 (55.3)	1	Reference
No	89 (59.3)	67 (44.7)	1.81	1.14 - 2.86
Previous benign breast disease*				
Yes	18 (12.0)	7 (4.7)	2.79	1.13 - 6.88
No	132 (88.0)	143 (95.3)	1	Reference

OR, odd ratio; CI; confidence interval; [a]univariate logistic regression test was used in obtaining P-values and the odd ratios
*P-value <0.05

and reproductive factors were shown Table 1. Late ages at menopause after 55 years old (OR 2.8, 95% CI 1.18–6.67), with history of menstrual irregularity (polymenorrhea, oligomenorrhea, or amenorrhea) (OR 3.2, 95% CI 1.00-10.08) or who never breastfed (OR= 1.74, 95% CI: 1.09 - 2.76, P=0.020) were significantly more likely to develop breast cancer. Nevertheless,

Table 2. Multivariate Analyses: Breast Cancer Risk Factors

Risk factor	B	OR[a]	95% CI[a]	P-value[a]
Factors associated with decreased breast cancer risk:				
Education >11 years	-0.91	0.4	0.18-0.90	0.027
Employed	-0.8	0.45	0.27-0.75	0.002
Breastfeeding > 1year	-0.7	0.5	0.28-0.90	0.022
Practice low fat diet	-0.64	0.53	0.32-0.87	0.013
Factors associated with increased breast cancer risk:				
Irregular Menstruation	1.45	4.25	1.14-15.80	0.031
First degree relative with cancer	1.08	2.95	1.14-7.60	0.025
Distant relative	1.04	2.84	1.01-7.90	0.046
Benign breast disease	0.89	2.43	0.93-6.42	0.072
OCP used	0.78	2.15	1.16-3.97	0.014

[a]Multivariate conditional logistic regression was applied for all variables with P values < 0.20 in the univariate logistic regression in order to obtain adjusted odd ratio: OR, odd ratios;; CI, confidence interval

no statistically significant associations were observed between breast cancer and age at menarche, number of children (parity), age at first full-term pregnancy, number of abortions and menopausal status.

Among all lifestyle factors and external factors studied (Table 1), only previous history of benign breast disease (OR=2.8, 95% CI: 1.13-6.88, P=0.026) and never practicing low fat diet (white meat, white fish, skinless chicken and avoiding deep fried food) (OR= 1.81, 95% CI: 1.14 - 2.86, P=0.011) significantly increased breast cancer risks. All variables were measured for controls up to the date of interview and for cases up to the date of diagnosis.

Multivariable Analyses

Among the factors further evaluated in the multivariable logistic regression analyses, history of menstrual cycle irregularity (adjusted OR= 4.94, 95% CI 1.14-15.8), history of benign breast disease (adjusted OR= 2.43, 95% CI 0.93-6.42), having first degree relatives with cancer (adjusted OR= 2.95, 95% CI 1.14-7.6) and distant relative with cancer (adjusted OR= 2.84, 95% CI 1.01-7.9) were found to be associated with breast cancer risk as statistically significant independent factors (see Table 2). Although, oral contraceptive use was not significantly related to breast cancer risk in the univariate analysis; it appeared as significant risk factors after controlling other confounders (OR 2.15, 95% CI 1.16–3.97).

On the other hand, factors including education (OR 0.4, 95% CI 0.18–0.9), occupation (OR 0.45, 95% CI 0.27–0.75), breastfeeding (OR 0.5, 95% CI 0.28-0.90) and practicing low fat diet (OR 0.53, 95% CI 0.32–0.87) were associated with decreased risk of developing breast cancer among our study population.

Discussion

We are aware that this hospital based study has some potential biases such as selection biases (non response bias, hospital admission bias, exclusion bias) and information bias (interview bias, recall bias, reporting

bias). On the other hand, General Penang Hospital is one of the busiest hospitals located in Penang state.

Breast cancer is usually considered as a disease of high socio-economic status [Krieger N, 1990]. This was contradictory with our results regarding educational status, while monthly income level was not significantly associated with breast cancer risk. In our study, higher level of education and having occupation were found to have a protective effect against breast cancer (P< 0.05), which is concordant with other studies (Daud, 2001; Ozmen et al., 2009).

This study disclosed that subjects with a family history of breast cancer had a significantly higher risk of breast cancer compared to those without a similar family history, which was consistent with other studies (Stephen 1997, Pharoah 1997). Subjects who had a family history of either first-degree relatives included sister, mother or daughter breast cancer or distant relatives, i.e. grandmother, granddaughter, aunt or niece, who had with breast cancer exhibit a three-fold excess risk (OR=2.95 and OR=2.84 respectively), compared to 1.5-2.1 in a meta-analytical study (Pharoah, 1997). Recall bias in this case-control design whereby breast cancer patients are more likely to remember a positive family history than controls, resulted in an overestimation in the effect size.

The current study detected a significant association between OCP use and breast cancer, which is consistent with other local studies [Norsa adah et al. 2005, Rejali et al.2007, Daud 2001] as well as international studies [Wang 1992, Brinton 1997]. However, most studies found no or weak association of OC use with the risk of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer). The association of OC use with breast cancer is related to the duration, dosage, pattern of usage, type of OC and the age of first use (McPherson 2000). This study could not measure the relationship of breast cancer with duration, type, dosage and pattern of OC usage because most of the subjects did not know or could not recall the details. Shapiro et al (2000) found that injectable hormonal contraceptives did not increase the risk of breast cancer. The association between breast cancer and other types of hormonal contraceptives via other routes, such as injection or implant also needs further research.

In agreement with earlier studies (Wang et al., 1992; Brinton, 1995; Bernstein, 1998; Fuberg et al., 1999; Newcomb et al., 1999), women who had never breastfed their babies were more likely to have breast cancer, even after controlling for covariates. The duration of breastfeeding also had an important influence. We found that the longer the lactation period, the lower the likelihood of getting breast cancer. This effect of lactation in breast cancer risk is comparable with another local study in Kuala Lumpur (Rejali et al., 2007) as well as with other international studies (Romieu et al.1996; Gilliland et al. 1998). As half of our study population is Chinese, this result also consistent with other studies conducted in China (Tao et al. 1988; Wang et al., 1992; Yuan et al. 1998). On the contrary of our findings Kelantan study (another state in Malaysia) (Norsa'adah et al., 2005) failed to find any significant association between breast cancer risk and breastfeeding. This may be related to the differences in racial distribution between Pinang and Kelantan states; where Malay are the major ethnic group and the fact that Malays women were more likely to practice prolonged breastfeeding compared to Chinese women (Tan, 2009). According to Second Report of National Health and Morbidity Survay, Ministry of Health, Malaysia, the national prevalence of breastfeeding was 88.6%, which was highest in Kelantan and among Malays.

Previous history of benign breast disease was highly significant in the present study (adjusted OR: 2.43). Similar finding was reported in Wang et al. study (adjusted OR, 2.40), whereas, no significant association was revealed in the other Malaysian studies [Norsa adah et al. 2005, Daud 2001]. Also, history of irregular menstrual cycle increased the risk of getting breast cancer dramatically (adjusted OR: 4.25); and this is supported by a Turkish study (Kuru et al., 2002) which found that menstrual irregularity increased the risk by 1.61 times.

Dietary factors are also suspected to play a role in the development of breast cancer. High intake of dietary fat and energy has been associated with higher occurrence of breast cancer in animal experiments and ecological comparisons between populations (Wynder et al., 1994). The fact that practicing low-fat diet exhibited an inverse relationship with the risk of breast cancer has been illuminated by this study (adjusted OR: 0.53). Red and fried meat consumption and fatty foods were suggested as important risk factors for breast cancer (Lima et al., 2008). Another cohort study (Byrne et al., 1996) reported a signi ficant relative risk (RR) of 1.7 for women who practiced eating the skin on poultry.

In summary, this study showed the importance of family histories of breast cancer, history of benign breast disease and menstrual irregularity on increasing the risk of breast cancer. Most importantly, the risk of the disease increased dramatically with OCP use, never breastfeeding and never practicing low fat diet. The findings of the current study suggest that the following strategies and preventive measures could well help in decreasing breast cancer prevalence in the study area:

Women with family history of breast cancer should be counseled and educated about their risk of getting breast cancer, and should be highly recommended to be involved in screening programs for early detection: 1) Launching campaigns and educational programs concerning the dietary habits and the importance of avoiding food with high fat contents, especially those who have already had other established risk factors. As well as campaigns that increase women's awareness related to practicing breastfeeding; 2) Preparing brochures that reveal the direct relationship between OCP uses and breast cancer risk.

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