

Exposure to Second-Hand Smoke Predicts Breast Cancer Occurrence among Malaysian Women

(Pendedahan kepada Asap Rokok Sekunder Meramalkan Kejadian Kanser Payu Dara dalam Kalangan Wanita di Malaysia)

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ABSTRACT

Breast cancer is the commonest type of cancer among Malaysian women. This study aimed to determine the associated factors for breast cancer occurrence among Malaysian women. A case-control study was conducted at primary cancer referral centre in the East Coast of Peninsular Malaysia from January 2014 to August 2015. Untreated breast cancer (n=55) were assigned as cases compared to healthy controls (n=58). Sociodemographic and reproductive data were collected using a standardized questionnaire while dietary data was obtained using validated diet history questionnaires (DHQ). Anthropometric assessments (weight, height, hip, waist circumference (WC) and body fat composition) were recorded. Overnight fasting venous blood samples were analysed for glucose levels, insulin, high sensitivity C reactive protein (hs-CRP), high molecular weight (HMW) adiponectin and lipid profiles. Simple logistic regression showed factors associated with breast cancer risk include age, lower education level, lower monthly household income and exposure to secondary smoke (sociodemographic factors), pulse rate, the use of more than one year of traditional medicine, systolic, and diastolic blood pressures (physical examination and reproductive factors) as well as WC, HDL cholesterol, TG, blood glucose, and sugar intake (nutritional status) were investigated. Multiple logistic regression showed factors associated with breast cancer risk included exposure to a second-hand smoke (OR=10.00, (95% CI: 2.42, 41.30)), low monthly household income (OR=18.05, (95% CI: 2.56, 127.10)) and high systolic blood pressure (OR=1.08, (95% CI: 1.04, 1.12)). Exposure to second-hand smoke, low monthly household income and high systolic blood pressures are predictors to breast cancer among Malaysian women.

Keywords: Breast cancer; low income; secondary smoke; systolic blood pressure

ABSTRAK

Kanser payudara adalah sejenis kanser yang paling biasa berlaku dalam kalangan wanita Malaysia. Kajian ini bertujuan untuk menentukan faktor yang berkaitan dengan kanser payudara dalam kalangan wanita Malaysia. Kajian kes-kawalan dijalankan di pusat rujukan primer kanser di Pantai Timur Semenanjung Malaysia dari Januari 2014 hingga Ogos 2015. Pesakit yang belum dirawat untuk kanser payudara (n = 55) diletakkan dalam kumpulan kes dibandingkan dengan kumpulan kawalan (n = 58). Data sosiodemografi dan reproduktif diperoleh melalui soal selidik piawai manakala data pemakanan diperoleh daripada soal selidik sejarah pemakanan yang disahkan (DHQ). Penilaian antropometri (berat, tinggi, pinggul, lilitan pinggang (WC) dan komposisi lemak badan) telah direkodkan. Sampel darah vena selepas puasa semalaman dianalisis untuk tahap glukosa, insulin, kesensitifan tinggi protein reaktif (hs-CRP), adiponektin berat molekul tinggi (HMW) dan profil lipid. Regresi univariat menunjukkan faktor berkaitan dengan risiko kanser payudara termasuk usia, tahap pendidikan rendah, pendapatan isi rumah bulanan yang rendah dan pendedahan kepada asap rokok sekunder

(faktor sosiodemografi), kadar nadi, penggunaan ubat tradisi lebih dari satu tahun, tekanan darah sistolik dan diastolik (pemeriksaan fizikal dan faktor reproduktif) serta WC, kolesterol HDL, TG, glukosa darah dan pengambilan gula (status pemakanan) dikaji. Regresi multivariat menunjukkan faktor yang dikaitkan dengan risiko kanser payudara termasuk pendedahan kepada asap rokok (OR = 10.00, (95% CI: 2.42, 41.30)), pendapatan bulanan isi rumah yang rendah (OR = 18.05, (95% CI: 2.56, 127.10)) dan tekanan darah sistolik yang tinggi (OR = 1.08, (95% CI: 1.04, 1.12)). Pendedahan kepada asap rokok, pendapatan isi rumah bulanan yang rendah dan tekanan darah sistolik tinggi adalah ramalan kanser payudara dalam kalangan wanita Malaysia.

Kata kunci: Asap rokok sekunder; kanser payudara; pendapatan rendah; tekanan darah sistolik

INTRODUCTION

The top five cancers affecting Malaysians in general are breast, colorectal, lung, cervical, and nasopharyngeal cancers (National Cancer Society Malaysia 2015). Breast cancer became the leading killer of women in Malaysia (25%), besides in the Philippines (23%), Indonesia (22%), New Caledonia, Vanuatu (both 21% each), Singapore (20%) and Samoa (13%) (Youlden et al. 2014). It occurs in both men and women although male breast cancer is rare. Additionally, breast cancer is the second most common cancer worldwide and is fifth ranked for being the main cause of death (Ferlay et al. 2015). Several Asian countries were reported to have rapid increase in breast cancer mortality rates particularly Malaysia (Youlden et al. 2014). Research into the causes of breast cancer has progressed to the point of risk markers to distinguish women at different risk levels resulting in modifiable and non-modifiable risk factors. To date, reported non-modifiable risk factors of breast cancer are age, family history, age at first full-term pregnancy, early menarche and late menopause. Modifiable factors that may affect the risk of cancer include dietary, physical activity, obesity, alcohol and environmental risk factor (National Cancer Institute 2012).

Numerous scientific reviews point to the potential role of active smoking in contributing to the development of breast cancer (Bennicke et al. 1996; Hrubá 2012; Reynolds 2013; Terry & Johnson 2003). However, the role of second-hand smoking on breast cancer development was less exonerated (Reynolds 2013). Non-smoker's continued exposure to secondary smoking could significantly increase breast cancer risk. This was proved by some studies from Japan, China and California but due to inconsistency outcomes, some studies rejected the evidence of this association (Hrubá 2012). For example, it was discovered that early breast cancer patients with ER+, HER2- had no clinically significant influence of

smoking on tumor characteristics and outcome (Goldvaser et al. 2017).

Our study provides an updated data of health status between breast cancer cases and healthy controls. Discursive parameters related to the risk factors of breast cancer occurrence were analysed throughout the study including health status, dietary intake, anthropometry measurement and body composition assessment. Besides, biochemical profiles of breast cancer and healthy controls such as glucose, lipid profiles, C-reactive profiles, insulin and adiponectin were examined. All these data add valuable information to the body of knowledge on contributing factors to breast cancer in Malaysia. The study also can stimulate more research inspirations especially in the aspect of intervention study towards breast cancer survivors. The comparison data discovered through this case-control study is important to elucidate the potential causative factors of breast cancer to create guidelines for breast cancer prevention among Malaysian women.

MATERIALS AND METHODS

Ethical approval was obtained from the Human Research Ethics Committee, Universiti Sains Malaysia (USM/KK/PPP/JEPeM[260.3.(21)] which complies with the Declaration of Helsinki. This is a case-control study which consisted of cases (untreated breast cancer cases) and ± 10 years' frequency-matched of age healthy women (controls) conducted at an oncology outpatient clinic of Hospital Universiti Sains Malaysia (HUSM) which is the primary cancer referral centre in the East Coast of Peninsular Malaysia. The inclusion criteria for both cases and controls were women aged 20 to 59 years old. Patients were recruited using a convenience sampling method from January 2014 until August 2015. Pregnant or lactating women were excluded. The cases included patients with histologically confirmed malignant breast cancer (stages I to IV) who have not undergone any chemotherapies

but were allowed to receive analgesics or undergo prior surgeries. The controls comprised of healthy volunteers from HUSM staffs with no medical illness, no known history of breast cancer or no active medication use.

Written informed consents were obtained from the respondents before face-to-face interviews were conducted using a set of questionnaires including a validated diet history questionnaire (DHQ). The validation was done among elderly (Suzana et al. 2020). However, this validated questionnaire was also being utilized among breast cancer patients (Suzana et al. 2010). The DHQ was built of a pre-coded dietary history with a qualitative food frequency questionnaire (FFQ). It was structured with local dietary habits of Malaysian and 18 food items from FFQ that habitually consumed by the study population. The respondents were measured for their heights (using a portable stadiometer), weights, body fat compositions (body composition analyzer: TANITA SC-330, Japan), waist circumference (WC) and hip circumference (non-extendible tape) (National Health and Nutrition Examination Survey (NHANES) 2013).

Additionally, fasting blood samples were also collected for biochemical tests after 10-12 hours overnight fasting. Serum samples were used to analyze the lipid biomarkers, high sensitivity C-reactive protein (hs-CRP), insulin and high molecular weight (HMW) adiponectin concentrations while plasma samples were used to measure fasting plasma glucose concentration. The blood samples were centrifuged at 4000 rpm for 10 min at 4 °C using an Eppendorf Centrifuge 5810R and were transferred into 1.5 mL microcentrifuge tubes. The samples were kept in -80 °C freezer before further laboratory analyses. Glucose determination was conducted by hexokinase/glucose-6-phosphate dehydrogenase method. TG, TC, HDL measurements were based on enzymatic colorimetric method while hs-CRP was based on the quantitative immunoturbidimetric method. Serum insulin concentration was based on quantitative chemiluminescent microparticle immunoassay method. HMW adiponectin were analysed using enzyme-linked immunosorbent assay (ELISA) kit (ALPCO, New Hampshire, USA).

In addition, the data on the patient's age, education level, exposure to second-hand smoke, monthly household income, vitamin use, systolic, and diastolic blood pressures, pulse rate, family planning and family history were also collected. Exposure to second-hand smoke is defined as the contact of passive smoke with the eyes, nose, mouth, throat, and the airways lining including the alveoli (Jaakkola & Jaakkola 1997).

Data analysis were done using an IBM SPSS statistics version 22.0 (USA). For descriptive result, numerical

and continuous data with normal distribution were presented as mean and standard deviation (SD) while skewed distributed data were presented as median and interquartile range (IQR). In addition, categorical data were presented as number and frequency. Associated sociodemographic, physical examination, reproductive factors, anthropometric, biochemical profiles, dietary intakes with breast cancer were analysed using a simple logistic regression.

Multiple logistic regression analyses were implemented to determine associated factors with breast cancer. Following a simple logistic regression, variables with p-values of less than 0.25 were selected at the preliminary variable selection stage into the multivariable model (Norsa'adah 2011). The significant variables were selected for inclusion in the multiple logistic regression by a stepwise forward selection procedure. The interactions and multi-collinearity problems between variables were checked in the final model which was further tested by using the Hosmer-Lemeshow goodness of fit test. The results of the simple logistic regression were presented as crude odds ratios (OR), while multiple logistic regression was presented as adjusted OR, confidence intervals (CI) and p-values. A p-value <0.05 was considered as statistically significant.

RESULTS

The mean (SD) age for breast cancer cases and healthy controls were 46.84 (7.87) years and 40.79 (9.78) years, respectively (Table 1). Malay was the dominant race in this study with a participation of more than 90% in both breast cancer cases and healthy controls which may reflect the local demographic population data in Kelantan. The simple logistic regression analysis of socio-demographic factors showed that age (OR: 1.08; 95% CI: 1.03-1.13; p=0.001), low education level (OR: 3.08; 95% CI: 1.43-6.64; p=0.004), exposure to second-hand smoke (OR: 3.36; 95% CI: 1.54-7.31; p=0.001) and low monthly household income of below RM 2,300 (OR: 13.18; 95% CI: 3.59-48.43; p<0.001) were significantly related to breast cancer development. As for the physical examination, the simple logistic regression analysis showed that pulse rate (OR: 1.06; 95% CI: 1.03-1.09; p<0.001), systolic (OR: 1.10; 95% CI: 1.05-1.15; p<0.001) and diastolic blood pressures (OR: 1.09; 95% CI: 1.04-1.14; p<0.001) were significantly related to breast cancer development. Additionally, simple logistic regression showed that more than a one-year post-partum practice of using CAM (p value= 0.037) significantly related to breast cancer development (OR: 9.62; 95% CI: 1.15-80.73; p=0.037).

TABLE 1. Baseline characteristics and its association with breast cancer

Variables	Cases (n=55)	Controls (n=58)	Crude OR (95% CI)	p-value*
Age (years) †	46.84 (7.87)	40.79 (9.78)	1.08 (1.03, 1.13)	0.001
Race				
Malay	51 (92.7)	55 (94.8)	0.70 (0.16, 3.26)	0.645
Chinese	4 (7.3)	3 (5.2)	1.00	
Marital status				
Married	52 (94.5)	50 (86.3)	1.00	
Single	3 (5.5)	8 (13.8)	0.20 (0.02, 1.74)	0.645
Education level				
Primary/secondary school	35 (63.6)	21 (36.2)	3.08 (1.43, 6.64)	0.004
University	20 (36.4)	37 (63.8)	1.00	
Exposure to second-hand smoke				
Yes	32 (58.2)	17 (29.3)	3.36 (1.54, 7.31)	0.002
No	23 (41.8)	41 (70.7)	1.00	
Monthly household income (RM) §				
<RM 2,300	31 (57.4)	4 (7.3)	13.18 (3.59, 48.43)	<0.001
RM 2,300-5,599	13 (24.1)	34 (61.8)	0.65 (0.24, 1.78)	0.403
>RM 5,600	10 (18.5)	17 (30.9)	1.00	
Chronic disease			-	-
Hypertension	7 (12.7)	0 (0)	-	-
None	48 (87.3)	58 (100)	-	-
Breast cancer stage			-	-
Stage 1	7 (12.7)	0.00	-	-
Stage 2	12 (21.8)	0.00	-	-
Stage 3	12 (21.8)	0.00	-	-
Stage 4	10 (18.2)	0.00	-	-
Unknown	14 (25.5)	0.00	-	-
Diagnosis period			-	-
0-6 months	43 (78.2)	0.00	-	-
7-12 months	9 (16.4)	0.00	-	-
13-18 months	2 (3.6)	0.00	-	-
>24 months	1 (1.8)	0.00	-	-
Surgery type			-	-
Lumpectomy	19 (34.5)	0.00	-	-
Partial mastectomy	1 (1.8)	0.00	-	-
Total mastectomy	22 (40.0)	0.00	-	-
Never	13 (23.6)			
Vitamins intake				
Yes	24 (43.6)	32 (55.2)	1.00	0.221
No	31 (56.4)	26 (44.8)	1.59 (0.76, 3.34)	
Alcohol intake				
Yes	1 (1.8)	1 (1.7)	1.06 (0.06, 17.30)	0.970
No	54 (98.2)	57 (98.3)	1.00	

Systolic (mmHg) [†]	133.89 (17.36)	118.12 (15.40)	1.06 (1.03,1.09)	<0.001
Diastolic (mmHg) [†]	82.49 (10.33)	71.79 (11.28)	1.10 (1.05,1.15)	<0.001
Pulse (bpm) [†]	84.44 (11.99)	75.48 (8.83)	1.09 (1.04,1.14)	<0.001
Menstruation cycle				
Normal	46 (83.6)	48 (82.8)	1.00	
Abnormal	9 (16.4)	10 (17.2)	0.94 (0.35, 2.52)	0.901
Age at menarche, years [†]	13.06 (1.28)	13.30 (1.43)	0.88 (0.66, 1.16)	0.345
Family planning				
Yes	28 (50.9)	37 (63.8)	0.59 (0.28, 1.25)	0.167
No	27 (49.1)	21 (36.2)	1.00	
Age during 1 st pregnancy (years) [†]	25.75 (5.23)	25.34 (2.66)	1.02 (0.93, 1.13)	0.631
Parity ^b	3.61 (2.03)	3.25 (1.97)	1.10 (0.91, 1.33)	0.335
Miscarriage				
Yes	18 (32.7)	23 (39.7)	0.74 (0.34, 1.60)	0.444
No	37 (67.3)	35 (60.3)	1.00	
Breastfeeding				
Yes	50 (90.9)	48 (82.8)	1.00	
No	5 (9.1)	10 (17.2)	0.48 (0.15, 1.51)	0.209
CAM intake				
<1 year	17 (30.9)	26 (44.8)	0.70 (0.32, 1.55)	0.376
>1 year	9 (16.4)	1 (1.7)	9.62(1.15, 80.73)	0.037
Never	29 (52.7)	31 (53.4)	1.00	
Menopausal status				
Premenopause	42 (76.4)	51 (87.9)	1.00	
Postmenopause	13 (23.6)	7 (12.1)	2.26 (0.83, 6.16)	0.113
1 st degree family history with breast cancer				
Yes	6 (10.9)	2 (3.4)	3.43(0.66, 17.77)	0.142
None	49 (89.1)	56 (96.6)	1.00	
2 nd degree family history with breast cancer				
Yes	9 (16.4)	5 (10.3)	1.70 (0.56, 5.13)	0.350
None	46 (83.6)	53 (89.7)	1.00	
Relatives with other cancer				
Yes	20 (36.4)	17 (29.3)	1.38 (0.63, 3.03)	0.425
None	35 (63.6)	41 (70.7)	1.00	

SD=Standard deviation; OR= Odds ratio; CI= Confidence interval; RM=Ringgit Malaysia

[†]Data are presented as frequency (percentage), unless otherwise indicated, [†]Data are presented as mean (SD)

^{*}p-value based on simple logistic regression test, [§]Based on the cut-off of the 10th Malaysia Plan (2011-2015)

The results of the simple logistic regression analyses of nutritional status including anthropometry, biochemical, and dietary assessments are presented in Table 2. Among all nutritional status factors analysed, waist circumference (OR: 1.05; 95% CI: 1.01-1.09; p=0.008), HDL cholesterol

(OR: 0.09; 95% CI: 0.02-0.36; p=0.001), TG (OR: 4.40; 95% CI: 2.04-9.50; p<0.001), glucose level (OR: 1.09; 95% CI: 1.04-1.14; p<0.001) (p=0.006) and sugar intake (OR: 1.56; 95% CI: 1.14-2.15; p=0.006) were significantly related to breast cancer development.

TABLE 2. Nutritional status and its association with breast cancer

Variables	Cases (n=55) Mean (SD)	Controls (n=58) Mean (SD)	Crude OR (95% CI)	p-value [†]
<i>Anthropometry assessments</i>				
Weight (kg)	60.10 (13.59)	60.05 (9.57)	1.00 (0.97, 1.03)	0.984
Height (cm)	152.53 (5.56)	153.45 (5.29)	0.97 (0.90, 1.04)	0.366
BMI (kg/m ²)	25.77 (5.53)	25.56 (4.19)	1.01 (0.94, 1.09)	0.815
WC (cm)	86.35 (11.42)	80.48 (10.59)	1.05 (1.01, 1.09)	0.008
HC (cm)	100.81(10.80)	100.12 (9.08)	1.01 (0.97, 1.05)	0.714
Fat mass (kg)	22.45 (10.99)	21.88 (7.12)	1.01 (0.97, 1.05)	0.742
Muscle mass (kg)	35.52 (4.21)	36.00 (3.03)	0.96 (0.87, 1.07)	0.483
Visceral fat rating	7.04 (3.17)	7.01(3.77)	1.00 (0.90, 1.12)	0.970
<i>Biochemical assessments</i>				
TC (mmol/L)	5.50 (1.13)	5.50 (0.99)	1.00 (0.70, 1.43)	0.992
HDL cholesterol (mmol/L)	1.36 (0.31)	1.57 (0.27)	0.09 (0.02, 0.36)	0.001
LDL cholesterol (mmol/L)	3.40 (0.96)	3.42 (0.88)	0.98 (0.65, 1.48)	0.920
TG (mmol/L)	1.74 (1.14)	1.11 (0.54)	4.40 (2.04, 9.50)	<0.001
Glucose (mmol/L)	6.72 (2.50)	5.41 (1.59)	1.56 (1.14, 2.15)	0.006
hs-CRP(mg/mL)*	2.50 (6.0)	2.05 (4.2)	1.02 (0.99, 1.05)	0.246
Insulin (μU/mL)*	5.35 (10.0)	6.10 (8.4)	1.00 (0.96, 1.03)	0.602
HMW adiponectin (μg/mL)	2.97(1.49)	3.54 (2.05)	0.84 (0.67, 1.05)	0.117
<i>Dietary assessments</i>				
Energy (kcal/day)	1443 (306.51)	1421 (249.38)	1.000 (0.999,1.002)	0.671
Protein (g/day)	54.81 (15.11)	54.53 (12.46)	1.001 (0.975,1.029)	0.914
Carbohydrate (g/day)	220.68 (46.09)	208.77(42.74)	1.006 (0.998,1.015)	0.157
Fat (g/day)	37.05 (12.06)	38.05 (11.01)	0.992 (0.961,1.025)	0.644
Saturated fat (g/day)*	4.85 (4.50)	3.65 (3.70)	1.067 (0.936,1.217)	0.330
MUFA (g/day)	5.95 (2.88)	6.12 (4.16)	0.987 (0.889,1.096)	0.803
PUFA (g/day)*	4.76 (3.70)	4.08 (2.80)	1.045 (0.929,1.176)	0.462
Potassium (mg/day)	959.16 (453.76)	899.07 (247.90)	1.000 (0.999,1.002)	0.392
Calcium (mg/day)	365.06 (187.34)	358.57 (147.35)	1.000 (0.998,1.002)	0.836
Phosphorus (mg/day)	928.98 (334.60)	983.36 (273.32)	0.999 (0.998,1.001)	0.343
Iron (mg/day)	12.44 (4.92)	12.08 (5.39)	1.014 (0.943,1.090)	0.709
Cholesterol (mg/day)	111.88 (62.03)	109.52 (50.12)	1.001 (0.994,1.007)	0.822
Thiamin (mg/day)	0.57 (0.21)	0.53 (0.20)	3.000 (0.483,18.615)	0.238
Riboflavin (mg/day)	0.80 (0.37)	0.76 (0.27)	1.430 (0.441,4.633)	0.551
Niacin (mg NE/day)	8.27 (2.55)	8.41 (3.45)	0.984 (0.871,1.113)	0.802
Folate (μg/day)*	57.09 (51.42)	58.08(46.32)	1.003 (0.994,1.013)	0.486
Vitamin A (μg/day)	622.07 (382.53)	672.38 (302.46)	1.000 (0.999,1.001)	0.740
Vitamin C (mg/day)*	51.60 (57.01)	47.21 (44.59)	1.003 (0.996,1.010)	0.355
Vitamin E (mg/day)	3.51 (2.56)	3.04 (2.14)	1.164 (0.945,1.435)	0.153
Selenium (μg/day)*	15.70 (21.70)	17.22 (13.93)	0.997 (0.968,1.026)	0.828
Dietary fiber (g/day)*	2.37 (2.10)	2.08 (1.70)	1.123 (0.866,1.456)	0.381
Sugar (g/day)	26.98 (16.32)	20.55 (14.39)	1.028 (1.002,1.055)	0.032

SD=Standard deviation; OR= Odds ratio; CI= Confidence interval; BMI=Body mass index; WC=Waist circumference; HC= Hip circumference; TC=total Cholesterol; HDL=high density lipoprotein cholesterol; LDL=low density lipoprotein cholesterol; TG=triglyceride; hs-CRP=high sensitivity C reactive protein; HMW=high molecular weight; MUFA=monounsaturated fatty acid; PUFA=polyunsaturated fatty acid; NE=niacin equivalent

* Data were presented as median (interquartile range), † p-value based on simple logistic regression

Since age, education level, exposure to second-hand smoke, low monthly household income, vitamin use, systolic and diastolic blood pressures, pulse rate, family planning, breastfeeding, more than one year CAM practise, menopausal status, first degree family history with breast cancer, WC, HDL cholesterol, TG, glucose, hs-CRP, HMW adiponectin, carbohydrate, thiamine, vitamin E and sugar

intake had p-value of less than 0.25 by univariable analysis, they were inserted in the multivariable model (Norsa'adah 2011). Referring to Table 3, exposure to second-hand smoke, low monthly household income and systolic blood pressure were associated with a higher risk of having breast cancer after all factors were included in the multiple logistic regression model.

TABLE 3. Factors associated with breast cancer risk (n=118)

Variables	Adjusted OR (95% CI)	Wald statistics (df)	p-value*
Exposure to second-hand smoke			
Yes	10.00 (2.42, 41.30)	10.13 (1)	0.001
No	1.00		
Monthly household income (RM)			
<RM 2,300	18.05 (2.56, 127.10)	8.44	0.004
RM 2,300-5,599	0.58 (0.13, 2.55)	0.52	0.469
>RM 5,600	1.00		
Systolic blood pressure	1.08 (1.04, 1.12)	13.75 (1)	<0.001

OR= Odds ratio; OR= Odds ratio; CI= Confidence interval; RM= Ringgit Malaysia

*p-value based on multiple logistic regression test

The model reasonably fits well. Model assumptions are met. There are no interaction and multicollinearity problems

Final model equation

Logit (P) = $\ln [P/1-P] = -20.027 + (2.303 * \text{exposure to second-hand smoke}) + (2.893 * \text{monthly household income of less than RM 2,300}) - (0.548 * \text{monthly household income of RM 2,300 to RM 5,599}) + (0.076 * \text{systolic})$

DISCUSSION

The present study indicated that there was significant CAM practice for more than one year during confinement for breast cancer patients. Nevertheless, the effectiveness of *Jamu* produced in Malaysia is not largely confirmed because the preparation is not based on phytopharmaceutical, but is widely homemade. Reliance on traditional alternative medicine with cheap cost is attributed to the slow presentation and the late stage diagnosis among patients predominantly coming from developing Asian countries (Agarwal et al. 2007).

In our study, interestingly, patients with breast cancer had higher body weight and BMI than the healthy controls. Obesity in women, regardless of their age, leads to more aromatase and more extra-glandular estrogen production which may lead to estrogen-receptor-positive (ER+ breast cancer). Estrogens are synthesized from

androgens by aromatase in the gonads and in peripheral tissues, principally, the adipose tissue (Beaber et al. 2014). The present study established significant differences between the breast cancer cases and healthy controls in WC. The visceral fat releases an abundant of adipokines, inflammatory markers and insulin-like growth factors. Each type of the biomarkers released are linked with the development of breast cancer (Chen et al. 2016). In fact, adipose tissue in obese breast shows increased macrophage recruitment and blood vessel formation even before carcinogenesis all of which can promote cancer formation (Arendt et al. 2013). Another study also showed that new vessel formation and macrophages are activated when circulating estrogens were increased which then could trigger the growth of tumor microenvironment (Iyer et al. 2012).

The HDL cholesterol level in this study among breast cancer cases were significantly lower (1.34 mmol/l) than

that for healthy controls (1.57 mmol/l). Dysfunctional HDL is formed due to inflammation of systemic and vascular in the body, leading to atherogenesis (Rosenson et al. 2016). The present study found that the mean TG among breast cancer cases was 1.76 mmol/l, which was significantly higher than that for healthy controls (1.10 mmol/l). High TG and low HDL-cholesterol may influence the abnormalities in insulin bioavailability in non-diabetic individuals which characterize the pre-diabetic state (Natali et al. 2017). A national data extracted from a Malaysia survey showed that although 91% of ≥ 18 years old adult were not diabetic, approximately 17.5% of respondents have known and undiagnosed diabetes mellitus (National Health and Morbidity Survey 2015). Higher level of fasting plasma glucose among breast cancer cases may be explained by the impaired fasting glucose.

As evidenced in this study, the energy intake of breast cancer patients and healthy controls were below that of the recommendation by Malaysia recommended national intake (RNI) (Ministry of Health Malaysia 2017) while the protein intake from both groups fulfilled the recommendation. The Malaysian Adult Nutrition Survey (MANS), showed that Malay women aged 18 to 59 years old had energy intake of 1884 kcal and 75 g of protein/day (Ahmad Ali et al. 2019). This may be explained by the high intake of animal products as protein, macronutrient of animal-based food which also exceeds the recommendation (Ministry of Health Malaysia 2017). Besides, red palm oil, the richest source of carotenoid is commonly used for cooking in Malaysia (Nagendran et al. 2000). The median intake of vitamin C among women in this study was also below the recommended cut-off of 70 mg/day (Ministry of Health Malaysia 2017). This result is most probably due to low intake of fruits and vegetables in their meals since the median fibre intake was low, consistent with previous study that showed 45% adults had daily dietary fibre intakes that are lower than deficient range (Ng et al. 2016).

Factors significantly associated with breast cancer is having 1) exposure to second-hand smoke, 2) low monthly household income and 3) a high systolic blood pressure. The study site took place in Kelantan, a state in the East Coast of Peninsular Malaysia which have been reported to have the highest prevalence (41%) of non-smokers exposed to second-hand smoke at home among all states in Malaysia (National Health and Morbidity Survey 2015). Being of the male gender is significantly associated with smoking and tobacco (Chua et al. 2013; Juman et al. 2011). Additionally, low prevalence of smoking in females as compared to males may be due to gender norms as well as traditional values among Malaysians who

tend to perceive that smoking is dangerous to the health (Hum 2016). The female gender also tends to believe that expenditure on tobacco is better channelled to other uses including for education, food and health care (Hum 2016). This finding was consistent with that of a recent study on non-smoking breast cancer women with lifetime exposure to passive smoking. In fact, exposure to second-hand smoke has been reported to have 1.27 (95% CI: 0.97, 1.66) (for women less than 20 years) and 2.64 (95% CI: 1.87, 3.74) (for women more than 20 years) times higher risk of breast cancer than unexposed women. In comparison, Caucasian women who have exposure to second-hand smoke both at work and home had 2.80 (95% CI: 1.84, 4.25) times higher risk of breast cancer compared with women who were never exposed to second-hand smoke (Strumylaite et al. 2017).

A prospective cohort study conducted in 50,884 women in United States and Puerto Rico with no breast cancer but had a sister who had been diagnosed showed that there were 3.6% women diagnosed with invasive breast cancer after a mean follow up duration of 6.4 years. Women with no breast cancer, who are exposed to second-hand smoke were 80% at higher risk compared to women who never smoke but was finally been diagnosed with invasive breast cancers. This study provides an evidence on the association of passive smoker with breast cancer (White et al. 2017). Similar with the present study, majority of the untreated breast cancer cases were non-smokers who were exposed to secondary smoke, but at the same time have no first degree family history of breast cancer, indicating that secondary smoke is significantly associated with breast cancer occurrence.

Tobacco smoke contains thousands of chemicals with at least 20 chemicals known to be mammary carcinogens. The chemicals are deposited in breast cells and are metabolically activated in the breast as well as the surrounding adipose tissues besides being detected in nipple discharge (Hrubá 2012). Previously, two hypotheses have been proposed to explain the association between breast cancer and smoking. First, smoking increases the risk of breast cancer due to a direct carcinogenic effect (Bennicke et al. 1996). On the other hand, nicotine present in cigarette smoke has a minimal protective effect on breast cancer occurrence due to its anti-oestrogenic activity (Hrubá 2012) as shown by a recent study in United States and Puerto Rico, both of which indicated that current smokers tend to experience menopause at earlier ages (White et al. 2017). Similarly, women exposed to second-hand smoke had 1.35 times (95% CI: 1.11-1.65) higher risk of breast cancer compared to passive smokers who were unexposed where women exposed who are passive

smokers at home had a 1.30 times (95% CI: 1.05, 1.61) higher risk than never-exposed women (Li et al. 2015).

A study conducted in Malaysia investigated the effect of religious beliefs on smoking behaviour. It seemed that there is a ruling in Islamic law (*fatwa*) on forbiddance of smoking due to its potential harm which tend to be supported by non-smokers as compared to smokers. Smoking cessation was difficult to be achieved by active smokers due to addictions (Ramadan et al. 2016). This might be the reason why the smoking forbiddance was not supported by smokers and lead to increase number of smoking environment.

Socio-economic status has previously been reported as an important factor influencing detection of cancer stage at presentation (Sprague et al. 2011). The present study also demonstrated that low monthly household income was significantly associated with breast cancer. The finding was confirmed in another population-based cohort study among women diagnosed with breast cancer in Wisconsin in which women with lower household incomes had significantly (OR=2.06 (95% CI: 1.03, 4.11), $p < 0.05$) higher risk of getting distant stage at breast cancer diagnosis. They also had 1.46 times higher risk (95% CI: 1.10, 1.92) of dying from breast cancer as compared to women who had higher household incomes. These were explained by lower use of screening mammography and communities with lower education (Sprague et al. 2011).

It has been reported that the level of health literacy (as defined by the ability to understand and utilise any health information) tend to decline with decreasing income (Andrus & Roth 2002). This means low health literacy is associated with poorer health performances and outcomes (Abdurrahman et al. 2017; Andrus & Roth 2002; Yip et al. 2014). Similar with the studied population, low health literacy may indirectly cause by low monthly household income among breast cancer cases. The finding is supported by a past research which confirmed that the association between income and health performances may not always be directly apparent, unless with the addition of health literacy (Guntzviller et al. 2017).

Besides 1) being a passive smoker and 2) coming from a lower socio-economic background, our study also indicated that 3) systolic blood pressure was significantly associated with breast cancer. In a case-cohort study, no significant association was found between blood pressure and the risk of developing breast cancer. Besides that, in an early stage breast cancer where patients were recruited and followed up over 2.8 years, blood pressure (one of the five components of metabolic syndrome) was not associated with the risk of breast cancer recurrence among Italian women (Schairer et al. 2017). Thus, the increase in

systolic blood pressure in the present study may possibly be influenced by breast cancer simply due to the extra stress of attending an oncology appointment in the hospital (Agnoli et al. 2015).

The strongest feature of this study was the use of study subjects from untreated and newly diagnosed breast cancer patients. The subjects were not exposed to any drug intervention or cancer therapy during data collection. Case control study is normally modelled to investigate if an exposure is associated with an outcome (Berrino et al. 2014).

Although the exact mechanisms comprised between biochemical marker and breast cancer risk remains unclear, increase level of total cholesterol, triglyceride and glycaemic load were documented to be associated with higher breast cancer risk (Rossi et al. 2014). However, no association between biochemical profile and breast cancer occurrence in this study. Even though no significant association between HMW adiponectin and breast cancer occurrence was established in this study, our findings are still important because the association of HMW adiponectin with breast cancer is under-reported in Malaysia.

Despite the strengths, the study also had several limitations. First, breast cancer cases were enrolled based on a convenience sampling technique. The application of non-probability sampling technique would not be an issue as this study did not aim to assess the prevalence of breast cancer. Secondly, this hospital-based case-control study consisted of breast cancer cases and frequency-matched healthy controls. Frequency matching had to be used due to the challenge in obtaining older age of healthy controls who do not take any medication to be matched with older breast cancer cases. Thirdly, it was challenging to obtain a large sample of cases as most of the breast cancer cases were emotionally unstable since many just discover about the disease during data collection.

The mean age at breast cancer diagnosis indicated that overall, breast cancer cases were significantly older than that for healthy controls. There was therefore some difficulty in matching the older aged cases with the controls. Recruitment of controls was done by posting an advertisement at every department in USM health campus. There was significant difference in the highest education level of primary and secondary schools between breast cancer cases and healthy controls as well as those associated with breast cancer. According to a study conducted in Malaysia on breast cancer awareness, education level contributes to health behaviour and knowledge level, since women of higher education level had significantly greater awareness on breast cancer (Norlaili et al. 2013).

CONCLUSION

In conclusion, this study showed that factors associated with breast cancer development in Malaysian women were secondary smoke exposure, low monthly household income and a high systolic blood pressure. In future, more clinical studies on steps to decrease the age of smoking initiation and determination of the most effective smoking cessation strategies are required (Strumylaite et al. 2017).

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