RESEARCH ARTICLE

Anthropometric and Reproductive Factors among Newly-Diagnosed Breast Cancer Patients and Healthy Women: A Case-Control Study

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Abstract

The objective of this case-control study was to determine anthropometric and reproductive factors associated with the development of breast cancer among women. Fifty-six newly diagnosed breast cancer patients were recruited from the Oncology Clinic, Universiti Sains Malaysia (USM), and 56 healthy female hospital employees were recruited as controls. Socio-demographic and reproductive data were obtained using a standard questionnaire. Anthropometric factors (body weight, height, body fat percentage, visceral fat and waist and hip circumference) were assessed. A high waist circumference (adjusted OR= 1.04, [95% CI: 1.00, 1.09]) and being more than 30 years of age at first full-term pregnancy (adjusted OR=3.77, [95% CI: 1.10, 12.90]) were predictors of breast cancer development. The results of this study indicate that weight and reproductive health management should be emphasized for breast cancer prevention in Malaysia.

Keywords: Case-control study - anthropometric factors - reproductive factors - breast cancer risk - Malaysia

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Introduction

Breast cancer is the most common cancer type in women not only in world but also in Malaysia (Lim et al., 2008; Siegel et al., 2013; Torre et al., 2015). To date, risk factors for breast cancer have been extensively researched in western countries, and several studies have found that changes in reproductive patterns and unhealthy lifestyles, such as obesity, are related to the increased incidence of breast cancer observed throughout the world in the past decade. Breast cancer risk is also associated with exposure to hormones produced by the ovaries, specifically endogenous oestrogen and progesterone (Yue et al., 2013).

Reproductive factors that increase the duration and levels of exposure to endogenous hormones stimulate cell growth and are related to increased breast cancer risk among women. These factors include early menarche, late menopause, older age at first pregnancy, and nulliparity (Cancer, 2012; Anderson et al., 2014). On the other hand, breastfeeding and a greater number of childbirths have been shown to protect against breast cancer (Anderson et al., 2014).

Obesity is a known risk factor for breast cancer for both pre- and post-menopausal women (Cecchini et al., 2012; Gaudet et al., 2014; Tamaki et al., 2014). The general consensus is that obese women have an increased risk for post-menopausal breast cancer (Garrisi et al., 2012; Biglia et al., 2013) and a decreased risk for premenopausal breast cancer (John et al., 2011; John et al., 2014). A recent study generated some conflicting data suggesting an increased risk of premenopausal breast cancer among obese women (Amadou et al., 2013a; Bandera et al., 2013; Biglia et al., 2013); however, this finding was not consistent. In addition, several biological studies support a positive relationship between obesity and breast cancer development. Obesity can impair multiple biologic pathways, including inflammation, insulin resistance, and synthesis of endogenous sex hormones (Bulun et al., 2012; Ray and Cleary, 2012).

Risk factors for breast cancer development have been extensively researched and reported in Western countries, but data from Asian countries, particularly Malaysia, remain scarce. Therefore, the aim of this study was to determine the anthropometric and reproductive factors associated with breast cancer development among newly diagnosed Malaysian breast cancer patients. Hopefully these data will provide essential information for health professionals to aid in the development of a public health programme for breast cancer prevention in Malaysia focused on weight and reproductive health management.

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Materials and Methods

This case-control study was conducted from February 2014 to June 2015 in Kelantan, Malaysia. The study was approved by the Human Research and Ethical Committee of Universiti Sains Malaysia (USM) and complies with the Declaration of Helsinki. Case (n=56) and control (n=56) recruitment was approved and was conducted at USM (USMKK/PPP/JEPem [260.3. (21)]). The cases were newly diagnosed women with histologically confirmed malignant breast cancer (stages I to IV) who had not yet received any therapy (except for analgesics and/or surgery) and had a Eastern Cooperative Oncology Group (ECOG) grade of 0 to 2 and/or a Karnofsky scale performance status of >70% (Oken et al., 1982). The cases and controls were women who were not pregnant or lactating during the study period. They were recruited by convenience sampling of patients aged 20 to 59 years.

Premenopausal status is defined as the phase of menstruation neither normal nor irregular period while post-menopausal status was defined as a permanent cessation of menstrual periods for at least 12 months (Edwards and Li, 2013). Age at menarche was self-reported and was defined as the chronological age (in years) when the individual had her first menses. Age at first full-term pregnancy was defined as the age of the participant at the time of her first pregnancy that resulted in a birth between 39 weeks 0 days and 40 weeks 6 days gestation (Spong, 2013). First degree relatives include the mother, sisters, and daughters, and second degree relatives include grandmothers, aunts, cousins, and granddaughters.

All participants were briefed on the study procedures and were asked to sign a written informed consent form if they agreed to participate. Participants underwent face-to-face interviews using a set of questionnaires to obtain information on their socio-demographic status, medical history, reproductive factors, and family history of breast cancer. Then, anthropometric measurements, including body height, weight, waist and hip circumference, body fat composition, and visceral fat, were performed.

A portable stadiometer (SECA, Germany) was used to measure body height to the nearest 0.1 cm. Body weight, fat composition, and visceral fat were determined using a body composition analyser (Tanita, Japan) which uses bioelectrical impedance analysis (BIA) technology. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m2) (WHO, 2015). Waist circumference was measured to the nearest 0.1 cm at the point midway between the costal margin and iliac crest in the mid-axillary line, and hip circumference was measured as the greatest circumference around the buttocks (National Health and Nutrition Examination Survey,

Table 1. Socio-Demographic and Reproductive Factors of the Participants

Socio-demographic factors	Cases (n=56)	Controls (n=56)	Crude OR[a] (95% CI)	p-value
Age (years), mean (SD)	47 (8)	42 (9)	1.07 (1.02,1.12)	0.003*
Marital status				0.192[b]
Married	53 (94.6)	48 (85.7)		
Single	1 (1.8)	5 (8.9)		
Divorced/widowed	2 (3.6)	3 (5.4)		
Monthly household income (RM) [c]				
≤4000	41 (73.2)	23 (41.1)	3.92 (1.77,8.69)	0.001*
>4000	15 (26.8)	33 (58.9)	1.00 (reference)	
1st degree relative with breast cancer				0.271[b]
Yes	6 (10.7)	2 (3.6)		
No	50 (89.3)	54 (96.4)		
2nd degree relative with breast cancer				
Yes	8 (14.3)	6 (10.7)	1.39 (0.45, 4.30)	0.569
No	48 (85.7)	50 (89.3)	1.00 (reference)	
Age at first full-term pregnancy (years)				
≤30	40 (76.9)	45 (91.8)	1.00 (reference)	
>30	12 (23.1)	4 (8.2)	3.38 (1.01,11.31)	0.049*
No. of children				
Nulliparous	4 (7.1)	7 (12.5)	0.56 (0.15,2.05)	0.38
1-2	11 (19.6)	9 (16.1)	1.19 (0.45,3.19)	0.726
>2	41 (73.2)	40 (71.4)	1.00 (reference)	
Age at menarche (years)				
≤12	19 (33.9)	20 (35.7)	0.92 (0.43,2.01)	0.843
>12	37 (66.1)	36 (64.3)	1.00 (reference)	
Menstrual cycle				
Regular	47 (85.5)	48 (85.7)	1.00 (reference)	
Irregular	8 (14.5)	8 (14.3)	1.02 (0.35,2.95)	0.969
Menopausal status				
Pre-menopausal	41 (73.2)	48 (85.7)	1.00 (reference)	
Post-menopausal	15 (26.8)	8 (14.3)	2.19 (0.85,5.69)	0.106
Breastfeeding practices				
Ever	51 (91.1)	47 (83.9)	1.00 (reference)	
Never	5 (8.9)	9 (16.1)	1.95 (0.61,6.25)	0.259

Note: RM= Ringgit Malaysia; SD= Standard deviation; OR= Odds ratio; CI= Confidence interval, [a]Odds ratio based on simple logistic regression test [b]p-value based on Fisher's exact test, [c]Cut-off based on the median value, *Significance level at alpha <0.05

2013). Waist and hip circumferences were measured using non-extensible tape (SECA, Germany) with the participant standing and breathing normally.

Statistical analyses were performed using SPSS for Windows version 22.0 (IBM SPSS, Chicago, IL, USA). Continuous numerical data were summarised as the means (standard deviation [SD]), and categorical data were presented as frequencies (percentages). Skewed numerical data were presented as medians (interquartile range [IQR]). Fisher's exact test was used to test associations between two categorical variables when the assumption of expected frequency was not met (small count >20%).

Multiple logistic regression analyses were performed to determine the factors associated with breast cancer risk. At the preliminary variable selection stage, variables with p-values <0.25 by simple logistic regression analysis were included in the multivariable model. A stepwise forward selection procedure was used to select significant variables for inclusion in the multivariable model. The interaction terms and multi-collinearity problem were included in the final model. The final model was tested for fitness using the Hosmer-Lemeshow goodness of fit test. The results are presented as crude and adjusted odds ratios (OR), 95% confidence intervals (CIs) and p-values. A p-value <0.05 was considered to indicate a statistically significant difference.

Results

The mean (SD) ages of the case and control groups were 47 (8) and 42 (19) years, respectively. Most of the participants were married and had no family history of breast cancer. The simple logistic regression analysis of socio-demographic factors (Table 1) showed that age (OR=1.07 [95% CI: 1.02, 1.12], p-value =0.003) and monthly household income (OR=3.92 [95% CI: 1.77, 8.69], p-value= 0.001) were significantly related to breast cancer development. The reproductive factors of the participants are shown in Table 1. Only an age of more than 30 years at first full-term pregnancy was significantly associated with breast cancer development (OR= 3.38, [95% CI: 1.01, 11.31], p-value =0.049). Number of children, age at menarche, menstrual cycle, menopausal status, and breastfeeding practices were not significantly related to breast cancer development.

The results of the simple logistic regression analyses of anthropometric factors are presented in Table 2. Among all anthropometric factors analysed, only waist circumference was significantly different between the two groups (OR= 1.05 [95% CI: 1.01, 1.09], p-value =0.006).

Multivariable analysis

Because age, marital status, waist circumference, age at first full-term pregnancy and menopausal status had p-values <0.25 by univariable analysis, they were included in the multivariable model. Among all factors included in the multiple logistic regression model, only waist circumference and age of more than 30 years at first full-term pregnancy were associated with an increased risk of breast cancer development in this study (Table 3). While controlling for age at first full-term pregnancy, a one cm increase in waist circumference increased the risk of breast cancer development by 1.04-fold. In contrast, while controlling for waist circumference, persons greater than 30 years of age at first full-term pregnancy had a 3.77-fold increased risk of breast cancer development.

Table 2. Anthropometric Factors of the Participants

Anthropometric factors	Cases (n= 56) Mean (SD)	Controls (n= 56) Mean (SD)	Crude OR[a] (95% CI)	p-value
Height (m)	152.7 (5.7)	151.1 (13.7)	1.02 (0.97, 1.06)	0.462
Weight (kg)	61.1 (13.7)	59.2 (8.8)	1.02 (0.98, 1.05)	0.365
Waist circumference (cm)	86.8 (11.4)	80.7 (10.3)	1.05 (1.01, 1.09)	0.006*
Hip circumference (cm)	101.4 (11.0)	98.9 (12.4)	1.01 (0.98, 1.05)	0.271
BMI (kg/m2)	26.1 (5.5)	25.8 (4.4)	1.02 (0.94, 1.09)	0.696
Fat percentage	36.0 (10.0)	35.8 (6.2)	1.00 (0.96, 1.05)	0.911
Visceral fat	7.3 (3.1)	7.1 (3.8)	1.01 (0.91, 1.13)	0.841

Note: BMI= Body mass index; SD= Standard deviation; OR= Odds ratio; CI= Confidence interval, [a]Odds ratio based on simple logistic regression test, *Significance level at alpha <0.05

Table 3. Factors Associated with Breast Cancer Risk by Multiple Logistic Regression Analysis

Variables	Regression coefficient (b)	Adjusted OR[a] (95%CI)	Wald statistic	p-value
Waist (cm)	0.04	1.04 (1.00, 1.09)	4.03	0.045
Age at first full-term pregnancy (years)				
≤30	0	1.00 (reference)		
>30	1.33	3.77 (1.10, 12.90)	4.42	0.035

Note: OR=Odds ratio; CI= Confidence interval, [a]Forward LR multiple logistic regression model was applied, Multicollinearity and interaction terms were checked and not found, Hosmer-Lemeshow test, (p=0.176), classification table (overall correctly classified, percentage=61.4%) and area under the ROC curve (64.7%) were applied to check model fitness

Discussion

Our study provides information on risk factors for breast cancer in Malaysia. The multiple logistic regression model showed that waist circumference and being more than 30 years of age at first full-term pregnancy are significantly associated with an increased risk of breast cancer development. Among all anthropometric factors used to measure obesity, only waist circumference was significantly associated with breast cancer development in this study (adjusted OR= 1.04, [95% CI: 1.00, 1.09]); however, this finding does indicate that obesity is an important risk factor for breast cancer development in Malaysia. Obesity is an established risk factor for breast cancer development among post-menopausal women (Garrisi et al., 2012; Biglia et al., 2013) and is inversely associated with breast cancer development among pre-menopausal women. However, some studies (Bandera et al., 2013; Biglia et al., 2013) have found a higher risk of breast cancer for obese than non-obese pre-menopausal women.

Studies have shown that the interaction between obesity and all dysregulated metabolic pathways, including aromatization activity in adipose tissues, can lead to increased oestrogen hormone synthesis (Anderson and Neuhouser, 2012; Simpson and Brown, 2013; Wang et al., 2015), insulin resistance (Duggan et al., 2010; Capasso et al., 2013), oxidative stress, and inflammation (Catsburg et al., 2014) and hyperactivation of adipokines. All of these factors contribute to breast cancer development among both post- and pre-menopausal women. However, in our study, a stratified analysis according to menopausal status was not performed due to the small number of post-menopausal women enrolled.

Waist circumference is an anthropometric measure of abdominal (central) obesity (Amadou et al., 2013b). Currently, the most accepted definition of abdominal obesity among adult Asian women according to the International Diabetes Federation is a waist circumference ≥ 80 cm (Grundy et al., 2005). We found that an increased waist circumference increases the risk of breast cancer development by one fold. Similarly, a study of Malaysian women found that an increased waist circumference increases the risk of breast cancer development by three fold (Shahar et al., 2010). Given the high prevalence of abdominal obesity among Malaysian women [60.2% (95% CI: 58.5, 61.8)] (National Health and Morbidity Survey, 2015) and the consistently observed increased risk of breast cancer with abdominal obesity, it should be monitored by health programmes in Malaysia.

Another study of pre-menopausal Hispanic women conducted in a Western country found a similar result of a positive association between waist circumference and breast cancer status (OR= 1.09 [95% CI: 1.02, 1.16]) (John et al., 2014). A case-control study of Indigenous Nigerian women also found that waist circumference has a positive association with breast cancer development (Ogundiran et al., 2012). Furthermore, one study showed a higher risk of mortality with increasing abdominal obesity (relative risk per 0.1 increase of 1.31 [95% CI: 1.17, 1.48]) (World Cancer Research Fund International, 2014), and the Health, Eating, Activity, and Lifestyle (HEAL) study confirmed that abdominal obesity is associated with an increase in overall mortality due to increased insulin resistance and inflammation (Arcidiacono et al., 2012; George et al., 2014).

A matched case-control study of women in Kelantan, Malaysia was conducted without stratification according to menopausal status showed a significant association between BMI and breast cancer risk (OR =2.1 [95% CI: 1.1, 3.9]; p-value= 0.011) (Norsa adah et al., 2005). Furthermore, a case-control study of a Bangladeshi population showed a strong significant association between BMI and premenopausal breast cancer status women who had a BMI ≥25 kg/m2 had a fivefold increased risk of breast cancer (OR= 5.2 [95% CI: 1.10, 24.9]; p-value =0.04) (Iqbal et al., 2015). Although BMI is routinely used to measure general obesity, it was not found to be significantly associated (crude OR=1.02 [95% CI: 0.94, 1.09]; p-value =0.696) with breast cancer status in the current study. This finding is plausible because the majority of breast cancer patients (73.2%) in this study were pre-menopausal women, and many previous studies (Cheraghi et al., 2012; Amadou et al., 2013a; Suzuki et al., 2013) have found a negative and inverse relationship between obesity and breast cancer among this group of women.

Age of more than 30 years at first full-term pregnancy was significantly associated with breast cancer in the current study (adjusted OR= 3.77 [95% CI: 1.10, 12.90]; p-value= 0.035), which is similar to the findings of a study of urban and rural Indian populations, which found that women aged ≥26 years had a 1.78-fold higher risk of breast cancer than women aged <20 years (95% CI: 1.32, 2.41) (Nagrani et al., 2016). Additionally, a study among Iranian women had similar findings: women aged more than 35 years had a four-fold higher risk of breast cancer (OR= 4.66 [95% CI: 1.09, 19.93]) (Sepandi et al., 2014). Epidemiological studies have demonstrated a protective effect of early full-term pregnancy against breast cancer development (MacMahon et al., 1970; Albrektsen et al., 2005). According to a landmark case-control study, women who were less than 20 years old at first full-term pregnancy had a 50% lower risk of breast cancer than nulliparous women (MacMahon et al., 1970).

Pregnancy is a protective factor against breast cancer women who become pregnant at an early age have a lower risk of developing breast cancer later in life (Meier-Abt and Bentires-Alj, 2014). In contrast, being over 35 years of age at the time of first full-term pregnancy increases the risk of breast cancer (Polyak, 2006). There are several possible hypothesis of the protective effect of early age pregnancy against breast cancer development. It has been suggested that early full term pregnancy involved the alterations in systemic hormone levels and local cellular interactions in the mammary gland (Meier-Abt and Bentires-Alj, 2014). Pregnancy causes extensive changes to the breasts, making breast cells less likely to multiply and less likely to form tumours, which may explain the protective effect of pregnancy in younger women. However, it is unclear why becoming a first-time mother at an older age has the opposite effect. It is plausible that after 35 years of age, breast tissue is more likely to have accumulated cells carrying cancer-causing mutations or clusters of abnormal cells with the potential to become cancerous under the influence of the pregnancy hormonal environment (Hilakivi-Clarke et al., 2006).

In this study, number of children, age at menarche, menstrual cycle, menopausal status, and breastfeeding practices were not significantly associated with breast cancer development. In contrast, a meta-analysis of more than 100 epidemiological studies conducted by the Collaborative Group on Hormonal Factors in Breast Cancer found that for every year decrease in age at menarche, there is a 5% increase in breast cancer risk (Cancer, 2012). A large cohort study reported that women who experience menopause at the age of 50-54 years were at risk of developing breast cancer and had a 38% higher risk (hazard ratio =1.38 [95% CI: 0.87, 2.19]) than women who experience menopause before 45 years of age (Horn et al., 2013).

Furthermore, in a meta-analysis of 17 studies, nulliparous women had a significantly higher risk for breast cancer than parous women (relative risk= 1.16 [CI, 1.04 to 1.26]) (Nelson et al., 2012). The same study also found that breast cancer risk is significantly lower for women with three or more childbirths than for nulliparous women (relative risk= 0.73 [95% CI; 0.61 to 0.87]) (Nelson et al., 2012). Another study found that breastfeeding for more than 12 months is associated with a slightly lower risk of breast cancer (Faupel-Badger et al., 2013). However, in our study, we did not find a significant association of childbirth or breastfeeding duration with breast cancer risk, which may have been due to our comparatively lower sample size. Another factor that could have impacted our results is the variable ethnic and reproductive patterns among different Malaysian regions; in the present study, the majority of breast cancer patients were of Malay ethnicity. The biological differences between study populations could also have resulted in the contradictory results between studies (de Almeida et al., 2015).

One limitation of the current study was recall bias as each participant had to recall her past reproductive history. Furthermore, as this was a hospital-based case-control study, some bias is possible because the findings may only apply to hospital patients. In conclusion, a larger waist circumference and age of more than 30 years at first full-term pregnancy are significantly associated with breast cancer development in Malaysia. Public health programmes that incorporate monitoring of these factors should be implemented to aid in breast cancer prevention in Malaysia.

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