RESEARCH COMMUNICATION

# Roles of Adiposity, Lifetime Physical Activity and Serum Adiponectin in Occurrence of Breast Cancer among Malaysian Women in Klang Valley

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## Abstract

**Background: Lack of physical activities throughout life is related to obesity and is a risk factor of breast cancer, however, the associations of these factors with adiponectin in the occurrence of breast cancer have not been well investigated. Objective: This study investigated the relationship between adiposity, lifetime physical activities and serum adiponectin as breast cancer risk factors among Malaysian women in Klang Valley, Malaysia. Design: A case-control study was carried out among 70 newly diagnosed breast cancer patients and 138 controls aged 29 to 65 years old in Klang Valley. Subjects: The inclusion criteria for both groups were not having menstruation for premenopausal women, no evidence of pregnancy, not lactating and no chronic diseases such as hypertension and diabetes at the time of data collection. In addition, the cases must be pathologically newly diagnosed with breast cancer (stage I to III) and not on any therapy for cancer, with the exception of surgery. The controls were matched with cases for age ± 5 years and menopausal status. Measurements: Subjects were interviewed to obtain information on socio-demography, health and reproductive history using a pretested questionnaire. Subjects were also asked on their engagement of physical activity since secondary school. Anthropometric parameters included height, weight, waist and hips were also measured. A total of 6 ml of fasting venous blood was drawn for analysis of serum adiponectin in duplicate using Linko Adiponectin ELISA Kit. Fasting blood glucose (FBG) and blood pressure were also measured. Results: Mean body mass index (BMI) among cases and controls were not significantly different (p>0.05) at 26.1 ± 4.8 kg/m2 and 25.3 ± 4.5 kg/m2, respectively. FBG among cases (6.3 ± 1.8 mmol/L) was higher than controls (5.6 ± 1.1 mmol/L) (p<0.05). Waist hip ratio (WHR) of cases (0.85 ± 0.07) was also higher than controls (0.80 ± 0.06) (p<0.05). Abdominal obesity (WHR >0.85) increased risk of breast cancer by three folds [Adjusted OR 3.3 (95%CI 1.8-6.2)] (p<0.05). Adiponectin level was inversely related to waist circumference (r=-0.510, p=0.000), BMI (r=-0.448, p=0.000) and FBG (r=-0.290, p=0.026). Adiponectin level in cases (11.9 ± 4.8 μg/ml) were lower than controls (15.2 ± 7.3 μg/ml) (p<0.05). A greater reduction of breast cancer risk was observed with the increasing level of serum adiponectin level according to percentiles (p<0.05). Subjects with mean serum adiponectin level at the highest quintile (>75th)(≥16.7 μg/ml) had 80% reduced risk of breast cancer [Adjusted OR 0.2 (0.0-0.6)](p<0.05). A higher percentage of cases (47%) had not engaged in any physical activity throughout life as compared to controls (19%)[Adjusted OR 3.7 (1.7-7.7)](p<0.001). Conclusions: Abdominal obesity and physical inactivity throughout life were associated with low serum adiponectin and breast cancer risk among subjects. Thus, it is essential for Malaysian women to be physically active and achieve a healthy waistline in order to increase serum adiponectin level and reduce breast cancer risk.**

**Key Words:** Case-control study - adiposity - adiponectin - lifetime physical activity - breast cancer risk

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## Introduction

Cancer is a frightful disease of the 20th century and the incidence is rising throughout the world. Malaysia is also facing the increasing incidence of breast cancer in women. In year 2000, there were 3,825 new cases and 1,707 total deaths of breast cancer patients in Malaysia (Abdullah and Yip, 2003). This figure had increased to 4,337 cases in the year 2002 (Lim and Halimah, 2004). Abdominal obesity has been shown to be correlated with breast cancer risk in Klang Valley of Malaysia (Rabeta et al., 2007). Adipose tissue was originally considered to be a storage site of excess energy in the form of triglycerides (Fujimoto et al., 2005). However it is now recognized

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that adipose tissue not merely a fat-storing tissue (Miyoshi et al., 2003), but also an endocrine organ that produces numerous proteins with broad biological activities (Lord et al., 2005), including adiponectin (Kang et al., 2007).

Adiponectin is a large-molecular-weight adipocyte-derived hormone involves in the regulation of glucose and fatty acid metabolism (Dvorakova-Lorenzova et al., 2006). It influences whole-body insulin sensitivity and protects arterial walls against the development of artherosclerosis (Polak et al., 2007). In the situation of obesity, insulin resistance has also been associated with the development of breast cancer, and decreased adiponectin levels have been hypothesised to underline the association between breast cancer and obesity, as well as insulin resistance (Mantzoros et al., 2004). Adiponectin can directly control cancer cell growth and reduction in plasma adiponectin levels could be a risk factor for breast cancer (Kang et al., 2005). Serum adiponectin level has been reported to be reduced among Taiwanese breast cancer patients as compared to controls (Chen et al., 2006).

Lifetime physical activities may also play a role in the development of breast cancer. A large prospective cohort among 90,509 French women supports a protective role of physical activities on breast cancer risk (Tehard et al., 2006). Physical activities may decrease risk of breast cancer through several possible mechanisms including change in hormone level, immune function and reduction in weight gain (Coldtiz et al., 2003). However, few studies have been carried out to comprehensively analyse the association between physical activity, adiposity and the level of adiponectin with the risk of breast cancer. Thus, this study was conducted to investigate the association between adiposity, lifetime physical activities and serum adiponectin level and breast cancer risk among Malaysian women in Klang Valley. This study is part of a larger study investigating association between lifestyle, adiposity, dietary and antioxidant status with breast cancer that had been reported earlier (Rabeta et al., 2007; Suzana et al., 2008).

## Materials and Methods

A case control study was conducted from January 2005 until Jun 2006 among newly diagnosed breast cancer patients, stage I to III and had not yet undergone any therapy for cancer yet, with the exception for surgery. The cases were patients at several hospitals and service centre for breast cancer around Klang Valley including Kuala Lumpur General Hospital, Universiti Kebangsaan Malaysia Medical Centre, Selayang Hospital, Kajang Hospital, Tengku Ampuan Rahimah Hospital and National Cancer Society. The study was approved by the Ethics Committee of the Ministry of Health of Malaysia and Universiti Kebangsaan Malaysia. Written informed consent was obtained from each subject prior to participation in the study. The inclusion criteria for both cases and controls were not on menstruation, neither pregnant nor lactating and not diagnosed with hypertension and diabetes mellitus at the time of the study. The controls were matched with cases for age ± 5 years and menopausal status and recruited using convenience sampling at several government and private offices and also residential areas in Klang Valley. Postmenopausal status was defined as the absence of menstrual bleeding for at least 12 months prior to participation in this study.

Subjects were interviewed for socio-demographic status; health-related practices and lifetime physical activities were obtained through a standardized pre-tested questionnaire by trained interviewers. Some reproductive data was extracted from medical records of the patients.

The lifetime physical activities questionnaire was modified from The Breast Cancer Comprehensive Questionnaire developed by the Office on Women's Health of the Institute for Survey Research Temple University, USA (The National Women's Health Information Centre: US Department of Health and Human Services Office on Women's Health, 1998). Subjects were asked to recall whether they had engaged or not in any exercises and physical activities (at least two hours a week for four months or more in one year) since they were 13 years old in secondary school until the day of data collection. Those who had not engaged in some exercises and physical activities listed in the questionnaire at least two hours a week for four months or more in one year were categorised as no lifetime physical activities.

Subjects were also measured for body weight and height using a calibrated digital scale (TANITA, Japan) and a portable stadiometer (SECA, Germany) to the nearest 0.1 kg and 0.1 cm, respectively. Waist circumference was measured halfway between the costal edge and iliac crest and hip circumference was measured as the greatest circumference around the buttocks (Lee and Nieman, 2007) using a measuring tape (Rockton, USA). All anthropometric measurements were carried out using standard techniques (Lee and Nieman, 2007). Body mass index (BMI) was calculated from the weight and height measurements.

Blood pressure was assessed using a digital sphymomanometer (OMRON Model T5, USA). A total of 6 ml fasting venous blood was obtained for a measurement of fasting blood glucose (FBG) and serum adiponectin. FBG was determined using a glucometer (Roche, USA). For serum adiponectin analysis, the sample was centrifuged at 3000 g and 4˚C at room temperature for 30 min. The serum obtained was stored at -20˚C prior to duplicate analysis using a Human Adiponectin Elisa Kit (ACRP30) (Linkco Research, USA), with a measurement range of 1.56 ng/ml to 100 ng/ml and the limit sensitivity of this assay was 0.78 ng/ml according to the standard method (Ebinuma et al., 2006).

Data were analyzed using SPSS software version 15.0 (Illinois, USA). Independent sample t-test was used to compare means of all variables measured. The p value less than 0.05 was considered as statistically significant. Chi-squared test was used to investigate associations between categorical variables. Crude Odds Ratio (OR) was also calculated using 2 by 2 table, without adjusting for other risk factors. Binary logistic regression for case-control data was used to estimate adjusted odds ratio for several confounding factors including age of first pregnancy, family history, smoking, alcohol, oral contraceptive pill (OCP) and hormone replacement

**Table 1. Socio-demographic and Economic Profiles of Cases** (N=70) **and Controls** (N=138)

| Variables | | Cases | Controls | OR (95% CI) | P value |
|---|---|---|---|---|---|
| Ethnic: | Malays | 43 (61) | 78 (57) | - | - |
| | Chinese | 12 (17) | 45 (33) | | |
| | Indians | 15 (22) | 15 (10) | | |
| Marital status: | | | | | |
| Single/Widowed | | 10 (14) | 20 (14) | 0.8 (0.2-2.6) | 0.678 |
| Married | | 60 (86) | 118 (86) | | |
| Living arrangement: | | | | | |
| Alone | | 5 (7) | 6 (4) | 1.7 (0.5-5.8) | 0.678 |
| Spouse/children | | 65 (93) | 132 (96) | | |
| Educational status: | | | | | |
| No schooling | | 3 (4) | 1 (1) | - | - |
| Primary school | | 25 (36) | 18 (13) | | |
| Secondary school | | 32 (46) | 87 (63) | | |
| Higher institution | | 10 (14) | 32 (23) | | |
| Employment: | Yes | 38 (54) | 105 (76) | 2.7 (1.5-4.9) | 0.002* |
| | No | 32 (46) | 33 (24) | | |
| Monthly Household Income (RM): | | | | | |
| <1,500 | | 15 (21) | 27 (19) | - | - |
| 1500-3000 | | 37 (53) | 63 (46) | | |
| >3000 | | 18 (26) | 48 (35) | | |
| Menarche age: | | | | | |
| <12 years | | 21 (30) | 38 (28) | 0.3 (0.0-2.3) | 0.201 |
| ≥ 12 years | | 49 (70) | 100 (72) | | |
| Family history: | Yes | 11 (16) | 20 (15) | 1.1 (0.5-2.4) | 0.815 |
| | No | 59 (84) | 118 (85) | | |
| Age of first pregnancy: | | | | | |
| ≥ 30 years | | 17 (27) | 12 (10) | 3.3 (1.5-7.5) | 0.004* |
| < 30 years | | 45 (73) | 105 (90) | | |
| Having children: | No | 7 (10) | 23 (17) | 0.6 (0.2-1.4) | 0.201 |
| | Yes | 63 (90) | 115 (83) | | |
| Lactation: | No | 15 (21) | 44 (32) | 0.6 (0.3-1.1) | 0.927 |
| | Yes | 55 (79) | 94 (68) | | |
| Menopausal Status: | | | | | |
| Pre- menopausal | | 49 (70) | 93 (67) | 0.9 (0.5-1.7) | 0.703 |
| Post- menopausal | | 21 (30) | 45 (33) | | |

*p<0.05, using Chi squared test [a]Multivariate analysis, adjusted for working status, age at first pregnancy, smoking, alcohol, OCP, HRT, family history, lactation and BMI

therapy (HRT). Multivariate adjusted ORs were accompanied by 95% Confidence Interval. Bivariate correlations with two-tailed test of significance using Pearson coefficients were also carried out to compare between two variables.

## Results

A total of 70 pathologically confirmed, newly diagnosed breast cancer (stage I to III) and 138 controls participated in the study. The mean age of cases and control were 47.3 ± 8.0 and 46.2 ± 6.5 years, respectively, ranging between 25 and 65 years. Malaysia is a country in South East Asia with three main ethnic groups, Malays, Chinese and Indian. Table 1 reveals that the ethnic compositions of the cases were 61% Malays, 17% Chinese and 22% Indians. Whilst, the ethnic compositions of the controls were 57% Malays, 33% Chinese and 10% Indians. These figures were consistent with the composition reported by the Department of Statistics, Malaysia (2006) of which the majority of Malaysian women were Malays (61.6%), followed by Chinese (29.5%) and Indians (8.9%).

**Table 2. Mean ± SD of Anthropometric and Health Parameters in Cases** (N=70) **and Controls** (N=138)

| Variables | Cases | Controls |
|---|---|---|
| Body weight (kg) | 62.3 ± 11.3 | 60.7 ± 10.8 |
| Height (cm) | 154.5 ± 0.1 | 155.0 ± 0.1 |
| BMI (kg/m2) | 26.3 ± 4.8 | 25.3 ± 4.5 |
| Waist circumference (cm) | 86.0 ± 11.6 | 78.4 ± 10.4[a] |
| WHR | 0.85 ± 0.0 | 0.80 ± 0.0[a] |
| FBG (mmol/L) | 6.3 ± 1.8 | 5.6 ± 1.1[a] |
| Systolic pressure (mmHg) | 121.7 ± 16.7 | 121.4 ± 17.1 |
| Diastolic pressure (mmHg) | 75.0 ± 11.3 | 77.8 ± 13.0 |
| Serum adiponectin (µg/l) | 11.9 ± 4.8 | 15.2 ± 7.3[a] |

[a]Significant differences with p<0.05 using independent samples t-test; BMI-Body Mass Index; WHR-Waist hip ratio; FBG-Fasting Blood Glucose

Most of the subjects were married or living with partner or others (93% of cases and 96% of controls) and had a monthly household income between RM1500 to RM3000 and had received education up to secondary school or higher education (60% cases and 86% controls). Sociodemographic and reproductive history of subjects were not associated with risk of breast cancer, with the exception of being unemployed [OR 2.7 (1.5-4.9)] and age of first pregnancy of more than 30 years old [OR 3.3 (1.5-7.5)](p<0.05), as shown in Table 1.

The mean BMI among cases (26.3 ± 4.8 kg/m2) and controls (25.3 ± 4.5 kg/m2) were not differed significantly, as shown in Table 2. However, waist circumference, waist hip ratio (WHR), fasting blood glucose (FBG) were significantly higher among cases than controls (p<0.05 for all parameters). Whilst, serum adiponectin level was significantly lower in cases as compared to controls (p<0.05). Subjects with abdominal obesity (53%)(WHR >0.85) were at a higher risk of breast cancer by three folds as compared to those with no abdominal obesity (25%) [Adjusted OR 3.3 (1.8-6.2)] (p<0.05). A greater reduction of breast cancer was observed with the increasing quintile of adiponectin level, with those at the highest quintile (>75th)(≥16.7 µg/ml) had 80% reduced risk of breast cancer [Adjusted OR 0.2 (0.0-0.6)], followed by the 50th -75th percentile (13.3-16.7 µg/ml)[Adjusted OR 0.6(0.3-1.7)], 25th-50th (9.0-13.3 µg/ml) [Adjusted OR 0.6 (0.2-1.5)] as compared to the reference, ie those at the lowest quintile < 25th percentile (≤ 9.0 µg/ml) (p<0.05).

There was an inverse relationship between serum adiponectin level and body weight (r= -0.443, p=0.000), BMI (r = -0.448, p = 0.000), waist circumference (r = -0.510, p = 0.000), FBG (r =- 0.290, p = 0.026) (Figure 1). Mean adiponectin among subjects who had engaged with physical activity was slightly higher (14.4 ± 6.8 µg/ml) than those who had not engaged with physical activity since schooling days (13.3 ± 6.6 µg/ml). However, this difference was not significant.

Based on the lifetime physical activity questionnaire, a higher percentage of cases (47%) had not engaged with any physical activity throughout lifetime (defined as involvement in at least two hours a week for four months or more in a year, since secondary school) than controls (19%) [Adjusted OR 3.7 (1.7-7.7)](p<0.001), as shown in Table 3. Significant associations were observed in not

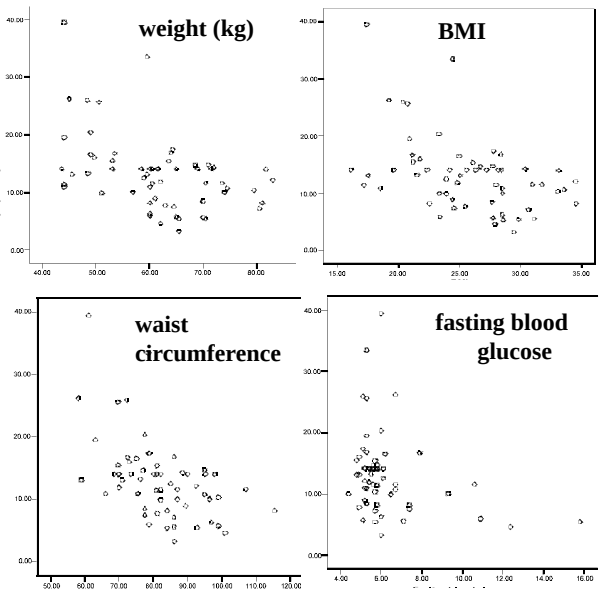


**Figure 1. Correlation of Serum Adiponectin Levels**. (a) Weight (r= -0.443, p=0.000), (b) BMI (r = -0.448, p = 0.000), (c) waist circumference (r = -0.510, p = 0.000) and (d) fasting blood glucose (r =- 0.290, p = 0.026) in inactive women

**Table 3. Subjects and Odds Ratios According to Lifetime Physical Activity History**

| Variables | Cases | Controls | Crude OR (95% CI) | Adjusted OR[a] (95% CI) |
|---|---|---|---|---|
| Lifetime physical history | | | | |
| No | 33 (47) | 26 (19) | 3.8 (2.0-7.2)** | 3.7 (1.7-7.7)** |
| Yes | 37 (53) | 112 (81) | | |
| Secondary school: Heavy intensity exercise | | | | |
| No | 42 (60) | 58 (42) | 2.1 (1.2-3.7)* | 1.2 (0.5-2.9) |
| Yes | 28 (40) | 80 (58) | | |
| Secondary school: Moderate intensity exercise | | | | |
| No | 56 (80) | 97 (70) | 1.7 (0.8-3.4) | 1.2 (0.4-3.2) |
| Yes | 14 (20) | 41 (30) | | |
| 18-24 years: Heavy intensity exercise | | | | |
| No | 59 (84) | 96 (70) | 2.3 (1.1-4.9)* | 1.7 (0.5-5.0) |
| Yes | 11 (16) | 42 (30) | | |
| 18-24 years: Moderate intensity exercise | | | | |
| No | 60 (86) | 99 (72) | 2.4 (1.1-5.1)* | 3.2 (0.9-10.4)* |
| Yes | 10 (14) | 39 (28) | | |
| 25-34 years: Heavy intensity exercise | | | | |
| No | 64 (91) | 99 (72) | 2.4 (1.1-5.1)* | 1.2 (0.3-4.4) |
| Yes | 6 (9) | 39 (28) | | |
| 25-34 years: Moderate intensity exercise | | | | |
| No | 58 (83) | 102 (74) | 1.7 (0.8-3.5) | 0.4 (0.0-1.3) |
| Yes | 12 (17) | 36 (26) | | |
| 35-44 years: Heavy intensity exercise | | | | |
| No | 68 (97) | 118 (86) | 5.8 (1.3-25.4)* | 2.4 (0.4-13.6) |
| Yes | 2 (3) | 20 (14) | | |
| 35-44 years: Moderate intensity exercise | | | | |
| No | 62 (89) | 104 (75) | 2.5 (1.1-5.8)* | 2.6 (0.7-9.8) |
| Yes | 8 (11) | 34 (25) | | |
| 45-54 years: Heavy intensity exercise | | | | |
| No | 69 (99) | 123 (89) | 7.6 (1.0-60.9) | 4.7 (0.5-47.2) |
| Yes | 1 (1) | 15 (11) | | |
| 45-54 years: Moderate intensity exercise | | | | |
| No | 65 (93) | 113 (82) | 2.8 (1.0-8.1) | 2.8 (0.8-10.5) |
| Yes | 5 (7) | 25 (18) | | |

*p<0.05 using Chi-squared test aMultivariate analysis, adjusted for working status, age at first pregnancy, smoking, alcohol, OCP, HRT, family history, lactation and BMI

being engaged with any heavy physical activity during secondary school, with Adjusted OR 2.1 (95% CI 1.2-3.7) (p<0.05); and moderate physical activity at the age of 18 to 24 years old [2.4 (1.1-5.1)] (p<0.05); heavy physical activity at 25 to 34 years old [Adjusted OR 2.6 (1.0-6.6)](p<0.05); and heavy and also moderate physical activity at the age of 35 to 44 years old, with Adjusted OR of 5.8(1.3-25.4)(p<0.05) and Adjusted OR 2.5(1.1-5.8)(p<0.05), respectively. Types of physical activity commonly engaged by subjects were netball, running and athletic events and volleyball, for heavy scale; and badminton, jogging, swimming and brisk walking for moderate physical activity.

## Discussion

The mean age of the cases in this study was consistent with the figure reported in the Second Report of The National Cancer Registry (NCR) in 2003 (Lim and Halimah, 2004). Majority of cases (76%) were in 40-59 years age group, as had been reported by the Second Report of the National Cancer Registry (NCR) (Lim and Halimah, 2004), of which breast cancer among Malaysian women occurred commonly in the 40 to 60 years old. Breast cancer is very rare in adolescents and very young women (Shanon and Smith, 2003). A study carried out in Kota Bharu Hospital at the East Coast of Malaysia indicated that from 75 cases recruited, 53.3% of the women were more than 40 years old and 38.7% were between 40 to 49 years old (Jaleel et al., 2006). However, the ethnic compositions of subjects in this study were not comparable to those reported by the NCR (Lim and Halimah, 2004), of which Chinese had the highest incidence with an age-standardized incidence rate (ASR) of 59.7 per 100,000 population, followed by Indians, with an ASR of 55.8 per 100,000 population and Malays with an ASR of 33.9 per 100,000 population. This was probably due to the fact that cases recruited in this study were mostly from Kuala Lumpur General Hospital, the government hospital which providing services to the lower socioeconomic group, predominantly Malays.

The present study found an inverse relationship between serum adiponectin level and body weight, BMI, waist circumference and FBG, supporting the evidences that obesity and insulin resistance were related to low adiponectin level (Lord et al., 2005; Miyoshi et al., 2003). Thus, obesity-related releases in adipocytokines results in low level of adiponectin has resulted in increased risk of breast cancer among the studied Malaysian women. This finding was consistent with the observation by Rose et al. (2004) that angiogenesis related to adipocytokine production played an important role in the development and progression of breast cancer, as adiponectin may decrease tissue fatty acid content and serum lipids (Jaleel et al., 2006). Earlier case control study among Japanese women by Miyoshi et al. (2003) has shown that breast cancer occurred in women with the low serum adiponectin levels. A later cohort study in USA also reported an inverse relationship between adiponecin and breast cancer risk, particularly in a low estrogen environment (Tworonger et al., 2007).

In the present study, abdominal obesity (waist circumference ≥ 80 cm) was also an important risk factor of breast cancer. Previous study has also found that women with visceral obesity have lower adiponectin levels, and hyperadiponectinemia may be the link with insulin secretion (Liu et al., 2006). Upper abdominal adiposity is commonly associated with hyperinsulinaemia insulin resistance (Vasudevan and Sreekumari, 2005) and in obesity, the number of receptors decreased and target tissue become less sensitive to insulin (Yamauchi et al., 2001). In addition, glucocorticoids hypersensitivity may be involved in the development of abdominal obesity and insulin resistance (Darmon et al., 2006). The effects of adiponectin on glucose and lipid metabolism are mediated by the adiponectin receptors, adipoR1 and adipoR2, which are mainly in liver and muscle (Jaleel et al., 2006; Morinigo et al., 2006). Thus, the prevalence of breast cancer in Western women was found to be increasingly parallel to that of visceral obesity and insulin resistance (Stoll, 2002) and the association between BMI and breast cancer might be more precise in the presence of adiponectin status or level (Chen et al., 2006). However, in a study among Sub-Saharan women, waist circumference does not predict circulating adiponectin level (Sobngwi et al., 2007), which is probably due to differences in study design and ethnicity.

Development of obesity was strongly related to sedentary life style (Bak et al., 2004). It is clearly observed in this study that physical inactivity throughout lifespan increased risk of breast cancer by two to five folds. A total of 22 from 27 studies reviewed by Friedenreich (2004) reported that women who were physically active had a lower risk of breast cancer compared to those who were not physically active. Physical activity would delay age at menarche, changed menstrual cycle and influenced ovarian hormone production, thus reduce breast cancer risk (Bernstein et al., 1995; Feigelson, 2003; Hankinson et al., 2004). Furthermore, a case control study by Adams-Campbell et al. (2001) indicated that heavy physical activity in adolescents reduced breast cancer risk among African-American women.

In conclusion, hypoadeponectinemia together with abdominal obesity and physical inactivity throughout life were important risks factor for breast cancer among Malaysian women. Further longitudinal study is required to determine the associations between physical activity and adiposity and breast cancer, with incorporation of other biomarkers of adiposity, glucocorticoids hormone and estrogens and also genetic polymorphism to provide better understanding of the pathogenesis of cancer among Asian women, including Malaysia. Undoubtfully, efforts should be made to disseminate a stronger public health message for Malaysian women to be more physically active since secondary school and obtain ideal body composition.

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