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The Malaysian Breast Cancer Survivorship Cohort (MyBCC): A Study Protocol

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Abstract

Introduction:

Over recent decades, the burden of breast cancer has been increasing at an alarming rate in Asia. Prognostic research findings from the Western countries may not readily be inferred to Asia, as the outcome of breast cancer depends on a multitude factors ranging from genetic, clinical, histological predictors to lifestyle and social predictors. The primary aim of this study is to determine the impact of lifestyle (e.g. nutrition, physical activity), mental and socio-cultural condition on the overall survival and quality of life among multiethnic Malaysian women following diagnosis of breast cancer. This study aims to advance the evidence on prognostic factors of breast cancer within the Asian setting. The findings may guide management of breast cancer patients not only during active treatment but also during the survivorship period.

Methods:

This hospital based prospective cohort study will comprise breast cancer patients (18 years and above) managed in the University Malaya Medical Centre (UMMC). We aim to recruit 1000 cancer survivors over a six-year period. Data collection will occur at baseline (within 3 months of diagnosis), 0.5-, 1-, 3-, and 6 years following diagnosis. The primary outcomes are disease free survival and overall survival, and secondary outcome is quality of life (QoL). Factors measured are demographic and socio-economic factors, lifestyle factors (e.g. dietary intake, physical activity), anthropometry measurements (e.g. height, weight, waist, hip circumference, body fat analysis), psychosocial aspects, and complementary and alternative medicine (CAM) usage.

Ethics and dissemination:

This protocol was approved by the UMMC Ethical Committee in January 2012. All participants are required to provide written informed consent.

Registration No: MEC No 896.150

Background

The past two decades observed a steep increase in the number of breast cancer incidence in most Asian countries [1-4]. However, this finding is in contrast to the Western countries whereby breast cancer incidences have stabilized or even decreased [5-7]. While early detection and new treatment regimes have both contributed to significant improvement in breast cancer survival rates in developed countries [8]. Mortality rates due to breast cancer have been escalating in most part of Asia, [9, 10]. Amidst economic improvement and Westernization of Asian countries, distinct changes are noticed in the lifestyle of women, reproductive factors and amount of exposure to environmental toxins [11-13]. Although it has been established that risk factors for breast cancer in Asian populations are similar to those in Western populations, additional prognostic factors such as ethnicity, physical activity, obesity, as well as nutritional factors/dietary intake may be different from that in Western countries [1, 11, 14]. In addition, the diverse Asian culture, religion, ethnicity and lifestyle also greatly influence breast cancer patients and affect their survivorship and quality of life [15, 16]. Body fatness has been frequently associated with increased risk of breast cancer and lower subsequent survival in the West [17] but little is known on the possible impact of obesity on survival following breast cancer within the Asian settings. Breast cancer survivors also tend to be younger in Asia than survivors in Western countries [18]. Thus the factors associated with breast cancer and survival may differ in Asian countries as to Western countries. It is therefore intriguing to understand the impact of tumor biology, lifestyle, health behavior, genetic and psychosocial factors on survivors' quality of life and overall survival of different ethnicities diagnosed with breast cancer in Asian settings.

Breast cancer is the most common cancer among Malaysian women [19]. Malaysia is a multiethnic country comprising three major ethnic groups. The highest population is represented by the Malays and subsequently followed by Chinese and Indians [20, 21]. Age standardized incidence rate of breast cancer is highest among the Chinese, followed by the Indians and lastly the Malay. However there are evidence that the Malay ethnic group observed the lowest five year overall survival compared to the Indians and Chinese. In multiethnic South East Asian settings, survival of women with breast cancer seems to be associated with ethnicity, independent of stage at diagnosis, tumor pathology and treatment [20-22]. Since ethnicity, culture and lifestyle are evidently entangled in Malaysia, breast cancer survivors can be a good source to identify association between these factors with and ethnicity. Likewise, this study will also establish probable associations between lifestyle, and psychosocial condition on disease free survival, overall survival, and quality of life after diagnosis of breast cancer. As such, the Malaysian Breast Cancer Survivorship Cohort (MyBCC) study is expected to provide evidence in improving the

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3 understanding of factors influencing breast cancer survivorship in multiethnic settings, and hence guide
4 the management of breast cancer survivors.
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10 **Objectives:**

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12 The primary objective of our study is to determine the association between socio-demographic and
13 lifestyle factors and overall survival as well as Quality of Life (QoL) among multiethnic breast cancer
14 survivors.
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17 Specific Objectives

- 18 1. To identify the ethnic differences in survival and QoL among Malaysian women after the
19 diagnosis of Breast Cancer.
- 20 2. To assess the impact of socio-economic inequality on survival and QoL among Malaysian breast
21 cancer survivors.
- 22 3. To determine if (change of) body composition impacts mortality of Malaysian women with breast
23 cancer.
- 24 4. To study the nutritional status and dietary intake among breast cancer survivors.
- 25 5. To determine the level of physical activity and its effect on survival upon breast cancer diagnosis.
- 26 6. To determine the prevalence and determinants of CAM use based on breast cancer survivors.
- 27 7. To determine the level of distress, anxiety and depression among breast cancer survivors.
- 28 8. To assess the financial difficulty and return to work (RTW) rate among breast cancer survivors.
- 29 9. To establish a biobank to store biospecimens to aid future research.

30 **Methods**

31 **Study Design**

32 This hospital based prospective cohort study will include newly diagnosed breast cancer patients
33 (age 18 years and above) managed in University Malaya Medical Centre (UMMC), Malaysia, who
34 provide written-informed consent to participate. The UMMC is a tertiary academic hospital, situated in a
35 relatively affluent part of Kuala Lumpur, and caters to a predominantly middle-class urban population.
36 Since 1993, this hospital established a prospective breast cancer registry. Based on a report of the
37 National Cancer Registry in 2006, UMMC managed approximately 10% of the newly diagnosed breast
38 cancer patients in Malaysia. Data on demography, clinical profile, pathological tumor characteristics and
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3 treatment will be obtained from the breast cancer registry. A base line anthropometric measurement and
4 body fat analysis will be conducted by trained research assistances. A survey in the form of questionnaire
5 will be conducted by trained interviewers at baseline and during half year, first year, third year and fifth
6 year follow-up period in order to collect information on variables such as quality of life, socioeconomic
7 status, physical activity, psychosocial support, return to work duration and CAM usage among breast
8 cancer survivors. Dietary assessment will be collected by dietitians.
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13 14 15 **Study Participants**

16 This study will include breast cancer patients diagnosed and managed in the UMMC from February 2012
17 onwards.
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20 21 **Eligibility Criteria**

22 **Inclusion Criteria**

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27 i. All women (18 years and above) who are newly diagnosed primary breast cancer (TNM stage 1-
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30 – From February 2012 to onwards
31 – Within 3 months of diagnosis
32 – In University Malaya Medical Center (UMMC).
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35 ii. Malaysian and can converse either in Malay, English, Mandarin, or Tamil.
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40 **Exclusion Criteria**

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42 i. Patients with prior history of any other cancer.
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44 ii. Ill patients who are unfit to participate in this study.
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47 **Ethics Approval**

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50 The study protocol and procedures were approved by the UMMC Ethical Committee, MEC Number
51 896.150. The patients will be informed and explained regarding the nature and the purpose of the study
52 verbally by the investigator. The patient has the right to refuse or disagree to participate in the study.
53 Trained research personnel will obtain written informed consent from study participants prior to their
54 enrollment and all collected information will be treated as confidential.
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Measures:

Exposure Measures:

The exposure of interests are demographic variables (e.g. age at diagnosis, ethnicity, age at marriage, age at first child birth, age at last child birth), socioeconomic variable (income, highest attained-education and occupation), anthropometric measurements (e.g. height, weight, waist hip circumference, percentage of body fat), diet (habitual food intake), use of any forms of CAM (e.g. used other type of treatment other than hospital treatment), physical activity, work related variables (type of work, working hour), health related variables (e.g. physical condition, appetite), and psychosocial variables (e.g. anxiety, depression) and biomarker (e.g. blood, tumor tissues).

Data on the exposure of interest will be obtained through personal interview (face-to-face), food diaries, anthropometric, and biological measurement. Details of which is described in Table 1.

Outcome Measures:

Patients will be monitored through follow-up in the breast cancer outpatient clinics in UMMC. Patients who are unable to attend clinics and those who are not scheduled for regular follow-up in UMMC, will be contacted by phone.

The primary outcome is overall survival. Data on mortality will be obtained from the hospitals' medical records, as well as active follow-up through the next-of-kin of patients. In addition, we will regularly update the vital status of patients through direct linkage with the National Registration Department (NRD), Malaysia, which holds the death records in Malaysia.

The secondary outcome is disease-specific survival where local and systemic recurrences are monitored and data are collected prospectively. The cohort will be followed up with scheduled phone calls and clinic visits in a systematic way to update patient's health status. Another secondary outcome is quality of life (QoL). QoL will be measured based on response of a quality of life questionnaires obtained from the European Organization for Research and Treatment of Cancer (EORTC). The EORTC QLQ-C30 comprised 30 items that includes five functional scales (physical, role, emotional, cognitive and social) and nine symptoms scale (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) and Global health status scale. On the other hand, the QLQ-BR23 is a more detailed questionnaire containing 23 items that comprises 23 questions designed for quantifying the quality of life of breast cancer patients. It includes five functional scales (body image, sexual functioning, sexual enjoyment, future perspective), and four symptoms scale (systemic therapy

side effect, breast symptom, arm symptom, upset by hair loss). Information from the questionnaires will be scored accordingly. The raw score for each subscale will be calculated and subsequently linear-transformed to 0 – 100 (standardized raw score) according to the guidelines of EORTC scoring manual. A higher score for functional scale represents a high/healthy level of functioning. A high score for the global health status/QoL represents a high QoL. However a high score for a symptoms scale represents a high level of symptom that indicates a worst quality of life.

Tools used for measures:

i. Anthropometry:

Body mass index (BMI), body fat percentage and waist hip ratio (WHR) will be used as indicators of body fatness. World Health Organization (WHO) definitions and classifications will be used. Patients' nutritional status will be measured from BMI, body fat analysis (BFA), WHR and food diaries. BMI and BFA will be measured at baseline and a subsequent follow-up at half year, first year, third year and fifth year period. WHR will be measured only during baseline period. BMI and BFA, body fat percentages will be measured using a portable body composition analyzer (TANITA BC-418 Body Composition Analyzer, Tokyo, Japan). This equipment will calculate body fat ratio, body fat mass, fat free mass, estimated muscle mass and Basal Metabolic Rate using data derived by using Bioelectric impedance analysis (BIA). Hydration status, recent physical activity, consumption of food or beverages, temperature, menstrual status, and body position are among the factors that can affect the validity and precision of the measurements. For example, subjects should avoid alcohol for and vigorous exercise for 12 hours before testing, so that body fluids are not perturbed prior to the measurements. The measurements should be taken on subjects approximately three hours after eating, and within 30 minutes of voiding.

ii. Food Diary:

Habitual food intake will be assessed using a self-administered three-day food diary. A qualified trained dietitian will provide information and give instruction on how to complete the three-day dietary records. The food diary will be generalized to all ethnic groups (Malays, Chinese and Indians). A mini food album detailing (multiethnic) Malaysian food items will be provided for their guidance. Subjects will be reassessed at two-years, and four-years after initial dietary assessment.

iii. Questionnaire:

Questionnaires will be used to obtain detailed information on concurrent illness, work related factors, complementary and alternative medicine (CAM) use, physical activity, and QoL (described in details in Table 1). Questionnaire for return to work self-efficacy scale (RTW-SE), readiness for return to work scale, and CAM use have undergone linguistic, content and face validation. Physical activity will be measured using the Global Physical Activity Questionnaire (GPAQ). Presence of anxiety and depression will be assessed using the Hospital Anxiety and depression Score (HADS). To measure QoL, two module will be used; EORTC QLQ-C30 and EORTC QLQ-BR23, which has been translated and validated to the local languages. The validity and reproducibility of EORTC QLQ-C30, GPAQ, and HADS had been proven to be satisfactory [23-25].

Table 1: Tools used in MyBCC study

Theme	Instruments
Demographic and socioeconomic characteristics	- Social - Economy background (Questionnaire)
Quality of Life	- European Organization for Research and Treatment of Cancer Core quality of Life questionnaire (EORTC QLQ-C30) - European Organization for Research and Treatment of Cancer Breast Cancer Quality of Life Questionnaire (QLQ-BR23)
Body weight and Nutrition	- Anthropometric measurement (BMI, WHR) - Food diary and mini food album
Physical Activity	- Global Physical Activity Questionnaire (GPAQ)
Complementary and alternative Medicine (CAM)	- CAM questionnaire
Psychosocial factors	- Hospital Anxiety and depression Score (HADS) & - Distress Thermometer (Questionnaire)
Work related factors	- Return to work self-efficacy scale (RTW-SE) - Readiness for return to work scale
Clinical, histological biological factors	- Clinical registry and Biobank

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3 **iv. Clinical registry:**

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5 There is already an established breast cancer registry in UMMC [11], which include data on
6 reproductive factors and family history; tumor characteristics i.e. size, grade, TNM stage,
7 receptor status (estrogen receptor, progesterone receptor, human epidermal growth factor receptor
8 2) and treatment details i.e. treatment modalities (surgery, radiotherapy, chemotherapy and
9 hormonal therapy). We will regularly link the current study variables to the registry.

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13 **Data Collection Point**

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15 **Baseline**

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17 At the time of recruitment to the study, the following baseline information will be recorded:

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- Demographic factors and clinical data
 - Information on the other illness/ co-morbidities
 - Detailed information on
 - ✓ Quality of life
 - ✓ Psychosocial factors
 - ✓ Work related factors
 - ✓ Physical activity
 - ✓ Complementary and alternative medicine use and
 - Biospecimen (blood, urine and tissues) will be preserved
 - BMI, WHR and BFA measurement

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40 **Follow-up**

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42 At the time of follow-up (half year, first year, third year and fifth year) during the study, the following
43 information will be recorded:

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- Clinical data and information on concurrent illness
 - Detailed information on
 - ✓ Quality of life
 - ✓ Psychosocial factors
 - ✓ Physical activity
 - ✓ Complementary and alternative medicine use
 - ✓ Work related factors
 - ✓ Food diaries (during 1st, 3rd and 5th year follow-up period) and

- BMI and body fat analysis (BFA) measurement

Figure 1 demonstrates the procedure for study recruitment and the overall flow of study design.

Data Analysis

Statistical Analysis

The results of survivor's demographics and baseline outcome variables will be summarized using descriptive summary measures, expressed as mean or median for continuous variables and proportions for categorical variables. We will report model coefficient for continuous outcomes, odds ratio (OR) for binary outcomes, or hazards ratio (HR) for time to event outcomes, with the corresponding 95% confidence intervals, and associated *p*-values. The Anova test will be conducted to determine the QoL score for each domain, according to respective cancer stages, *P* value <0.05 will be considered to be statistically significant.

Important prognostic factors will be identified by fitting the Cox's proportional hazard model. Overall survival will be estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariable Cox regression analysis will be used to estimate the relative risk of all-cause mortality associated with the various prognostic factors that we are studying. We will also assess whether ethnicity modifies the association between various prognostic factors and overall survival, as well as QoL. We will perform all analysis using Statistical Package for Social Sciences version 17.0 (SPSS Inc, Illinois).

Statistical Power

We estimate that we will be able to recruit about 1000 women during the six years of enrolment i.e. 150-200 patients per year in UMMC. With reports showing Malaysia to have the highest prevalence of obesity in Asia [26], we hypothesize that change in body weight may explain most of the survival disparities associated with lifestyle. Previous studies in UMMC recorded a mean BMI of breast cancer patients at diagnosis as 23.8 kg/m² (SD 4.12) and that the overall five year survival is 75% [20, 21]. A Cox regression of the log hazard ratio on BMI of these women with a standard deviation of 4 kg/m² based on a sample of 1000 participating women achieves an output of 90% statistical power at a 5% significance level to detect a regression coefficient of BMI (kg/m²) equivalent to 0.0468.

Discussion

Prognosis of breast cancer among Asian women are considerably different from Western women as lifestyle, socioeconomic profile, health believes, culture and genetic backgrounds are diverse [10]. Previous studies in selected populations (Malaysian) suggested that ethnicity is an independent prognostic factor of breast cancer survival [21]. Development of biomarkers for prognosis, expanding biobank and furthermore outcome measures and quality of life measures among cancer survivors are relatively scarce in Asia.

To the best of our knowledge, this study is the first in a multiethnic Asian setting to determine the association between socio-demographic and lifestyle factors on overall survival and Quality of Life (QoL) in breast cancer survivors. Notably, previous cohort studies [11, 27] only conducted survival analysis utilizing clinical data. Results from our study can provide imminent insights into association between patient's nutrition, BMI, physical, mental and socioeconomic status, on their quality of life and overall survival. We will also be able to assess the influence of ethnicity on these associations. A major strength of this study will be that we are using well-validated and reliable tools (i.e. accelerometer and portable TANITA) [28-30] to measure modifiable risk factors (i.e. physical activity, BFA). This study will add evidence on the impact of body fatness and its changes on overall survival and quality of life of Asian women following the diagnosis of breast cancer. In addition, there will be long-term storage of patient's blood, serum, plasma, urine and tissues in the UMMC Biobank for future research.

There are some limitations to the current study. It is expected that there will be some ambiguity in assessing the overall improvement or decrement in quality of life of the survivors, as perception varies from one individual to another. Nevertheless the validity and reproducibility of QoL was satisfactory [24] and adopted from the European Organization for Research and Treatment of Cancer (EORTC). Given that we have chosen to address a cohort comprising mostly of urban residents attending a tertiary hospital, our findings may not necessarily reflect the overall situation of breast cancer survivors in Malaysia. Another limitation is that we will be using a three-day food diary that depends on the respondent's full co-operation. However, diet history will be taken from two weekdays and one weekend and as such should reflect more valid estimates of patient's habitual dietary intake [31].

On the basis of the cohort study proposed here, this knowledge will be important for developing an effective strategy for the improvement of the overall survival and quality of life of breast cancer patients in middle-income countries such as Malaysia, whereby resources for health care are limited. This study will enable relevant parties to address prognostic factors that affect survival and enable a thorough focus to be placed on differences among ethnicity. Hence, we hope results from our

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3 study will contribute to the advancement in evaluation and appraisal methods for assessment of
4 prognostic factors in breast cancer. In the long run, we aim to improve the survival and quality of life
5 following the diagnosis of breast cancer in Asian women.
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11 **Acknowledgement**

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14 We thank the doctors, nurses, technical staff, and hospital administration staff at UMMC for the daily
15 administration of the Malaysian Breast Cancer Survivorship Cohort Study.
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18 **Members of MyBCC working group**

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21 Taib NA, Bhoo-Pathy N, Su TT, Majid HA, Nahar AM, Ng CG, Dahlui M, and Hussain S, from
22 University of Malaya, and Cantwell M, and Murray L from Queen's University Belfast
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28 **Footnotes**

29 **Contributors**

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32 NAT, TI, NB, and TTS are the principal investigators who designed the study and drafted the manuscript.
33 MD, LM, HAM, and AMN have made substantial contributions to the conception and design of the
34 project; NCG, MC and SH have been involved in drafting the manuscript. TI and NB are in charge of the
35 statistical analysis. All authors critically revised the manuscript for important intellectual contents and
36 provided the approval of the final version to be published.
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46 Research Grant (UM.C/HIR/MOHE/06) from the Ministry of Higher Education Malaysia.
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49 **Competing interest**

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52 We have no competing interests to declare.
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55 **Ethics approval**

56 This protocol was approved by the local Ethics committee of UMMC in January 2012.
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Provenance and peer review

Not commissioned; externally peer reviewed

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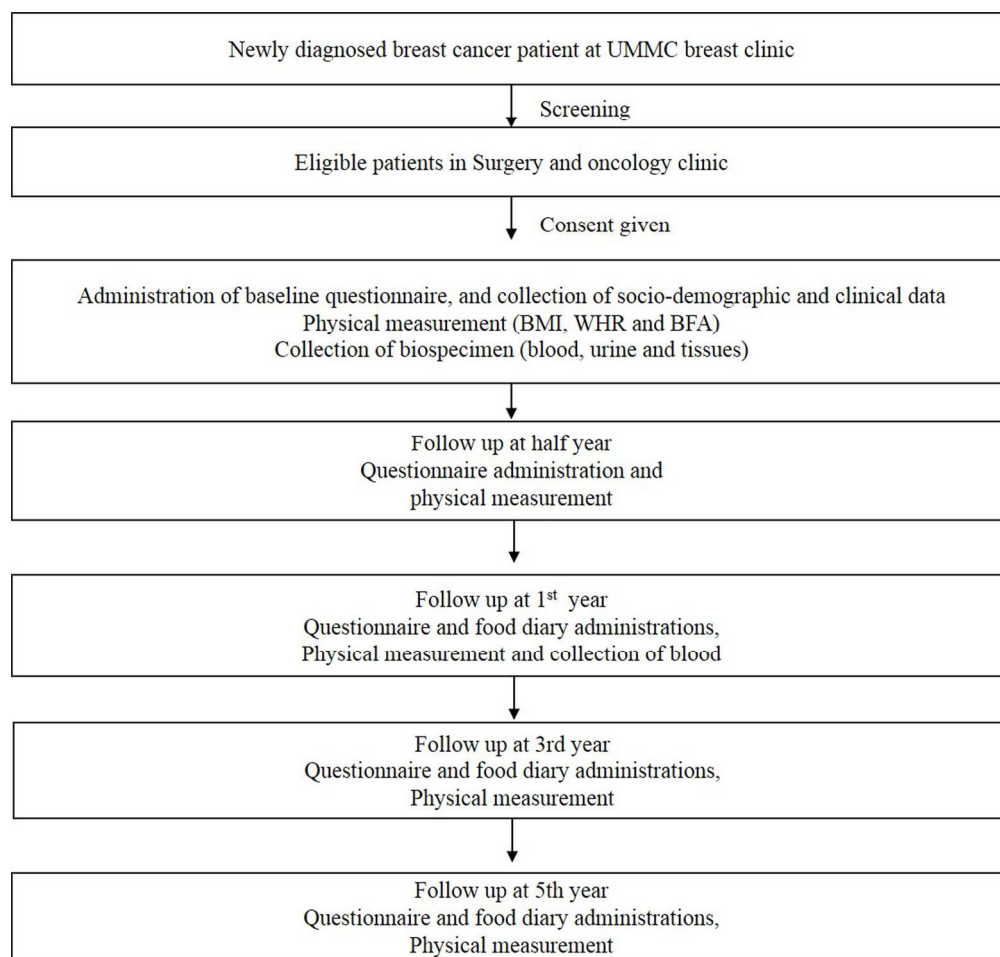


Figure 1. Flowchart of study recruitment process and overall study design
187x179mm (300 x 300 DPI)

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The Malaysian Breast Cancer Survivorship Cohort (MyBCC): A Study Protocol

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The Malaysian Breast Cancer Survivorship Cohort (MyBCC): A Study Protocol

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Abstract

Introduction:

Over recent decades, the burden of breast cancer has been increasing at an alarming rate in Asia. Prognostic research findings from the Western countries may not readily be inferred to Asia, as the outcome of breast cancer depends on a multitude of factors ranging from genetic, clinical, and histological predictors to lifestyle and social predictors. The primary aim of this study is to determine the impact of lifestyle (e.g. nutrition, physical activity), mental and socio-cultural condition on the overall survival and quality of life among multiethnic Malaysian women following diagnosis of breast cancer. This study aims to advance the evidence on prognostic factors of breast cancer within the Asian setting. The findings may guide management of breast cancer patients not only during active treatment but also during the survivorship period.

Methods:

This hospital based prospective cohort study will comprise breast cancer patients (18 years and above), managed in the University Malaya Medical Centre (UMMC). We aim to recruit 1000 cancer survivors over a six-year period. Data collection will occur at baseline (within 3 months of diagnosis), 0.5-, 1-, 3-, and 6 years following diagnosis. The primary outcomes are disease free survival and overall survival, and secondary outcome is quality of life (QoL). Factors measured are demographic and socio-economic factors, lifestyle factors (e.g. dietary intake, physical activity), anthropometry measurements (e.g. height, weight, waist, hip circumference, body fat analysis), psychosocial aspects, and complementary and alternative medicine (CAM) usage.

Ethics and dissemination:

This protocol was approved by the UMMC Ethical Committee in January 2012. All participants are required to provide written informed consent. The findings from our cohort study will be disseminated via scientific publication as well as presentation to stakeholders including the patients, clinicians, public, and policymakers via appropriate avenues.

Registration No: MEC No 896.150

Background

The past two decades observed a steep increase in the number of breast cancer incidence in most Asian countries [1-4]. However, this finding is in contrast to the Western countries whereby breast cancer incidences have stabilized or even decreased [5-7]. While early detection and new treatment regimes have both contributed to significant improvement in breast cancer survival rates in developed countries[8], mortality rates due to breast cancer have been escalating in most part of Asia, [9, 10]. Amidst economic improvement and Westernization of Asian countries, distinct changes are noticed in the lifestyle of women, reproductive factors and amount of exposure to environmental toxins [11-13]. Although it has been established that risk factors for breast cancer in Asian populations are similar to those in Western populations, the prognostic factors may be different from that in Western countries; ethnicity, physical activity, obesity, as well as nutritional factors/dietary intake [1, 11, 14]. In addition, the diverse Asian culture, religion, ethnicity and lifestyle may also influence breast cancer patients and affect their survivorship and quality of life [15, 16]. Body fatness has been frequently associated with increased risk of breast cancer and lower subsequent survival in the West [17] but little is known on the possible impact of obesity on survival following breast cancer within the Asian settings. Breast cancer survivors also tend to be younger in Asia than survivors in Western countries [18]. Thus the factors associated with breast cancer and survival may differ in Asian countries as to Western countries. It is therefore intriguing to understand the impact of lifestyle, health behavior, genetic, tumor biology, and psychosocial factors on quality of life and overall survival of women from different ethnic groups diagnosed with breast cancer in Asian settings.

Breast cancer is the most common cancer among Malaysian women [19]. Malaysia is a multiethnic country comprising three major ethnic groups. The highest population is represented by the Malays and subsequently followed by Chinese and Indians [20, 21]. Age standardized incidence rate of breast cancer is highest among the Chinese, followed by the Indians and lastly the Malay. However there are evidence that the Malay ethnic group observed the lowest five year overall survival compared to the Indians and Chinese. In multiethnic South East Asian settings, survival of women with breast cancer seems to be associated with ethnicity, independent of stage at diagnosis, tumor pathology and treatment [20-22]. Since ethnicity, culture and lifestyle are evidently entangled in Malaysia, breast cancer survivors can be a good source to identify association between these factors with and ethnicity. Likewise, this study will also establish probable associations between lifestyle, and psychosocial condition on disease free survival, overall survival, and quality of life after diagnosis of breast cancer. As such, the Malaysian Breast Cancer Survivorship Cohort (MyBCC) study is expected to provide evidence in improving the

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3 understanding of factors influencing breast cancer survivorship in multiethnic settings, and hence guide
4 the management of breast cancer survivors.
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10 **Objectives:**

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12 The primary objective of our study is to determine the association between demographic, socio-economic
13 status, lifestyle factors (dietary intake, physical activity), body composition, psychosocial factors, return
14 to work, as well as complementary and alternative medicine use, and overall survival as well as Quality of
15 Life (QoL) among multiethnic breast cancer survivors.
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20 Specific Objectives

- 21
22 1. To identify the ethnic differences in survival and QoL among Malaysian women after the
23 diagnosis of Breast Cancer.
- 24
25 2. To assess the impact of socio-economic inequality on survival and QoL among Malaysian breast
26 cancer survivors.
- 27
28 3. To determine if (change of) body composition impacts survival and QoL of Malaysian women
29 with breast cancer.
- 30
31 4. To study the nutritional status and dietary intake among breast cancer survivors and its impact on
32 survival and QoL.
- 33
34 5. To determine the level of physical activity and its effect on survival and QoL among breast
35 cancer survivors.
- 36
37 6. To determine the prevalence and determinants of CAM use and its impact on survival and QoL
38 based on breast cancer survivors.
- 39
40 7. To determine the level of distress, anxiety and depression and its effect on survival and QoL
41 among breast cancer survivors.
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43 8. To assess the financial difficulty and return to work (RTW) rate and its effect on QoL among
44 breast cancer survivors.
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51 We hypothesize that, the demography, socio-economic status, lifestyle (i.e. nutrition, physical activity),
52 body compositions, work related and psychosocial factors and complementary and alternative medicine
53 use of the different ethnic groups, will impact the overall survival and quality of life of Malaysian breast
54 cancer patients.
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Methods

Study Design

This hospital based prospective cohort study will include newly diagnosed breast cancer patients (age 18 years and above) managed in University Malaya Medical Centre (UMMC), Malaysia, who provide written-informed consent to participate. The UMMC is a tertiary academic hospital, situated in a relatively affluent part of Kuala Lumpur, and caters to a predominantly middle-class urban population. Since 1993, this hospital established a prospective breast cancer registry. Based on a report of the National Cancer Registry in 2006, UMMC managed approximately 10% of the newly diagnosed breast cancer patients in Malaysia. Data on demography, clinical profile, pathological tumor characteristics and treatment will be obtained from the breast cancer registry. A base-line anthropometric measurement and body fat analysis will be conducted by trained research assistants at around time of diagnosis (within 3 months of diagnosis). Figure 1 demonstrates the procedure of study recruitment and the overall flow of study. A survey in the form of questionnaire will be conducted by trained interviewers at around time of diagnosis (baseline) and at half year, first year, third year and fifth year follow-up period in order to collect data on quality of life, socioeconomic status, physical activity, psychosocial support, return to work duration and complementary and alternative medicine usage among breast cancer survivors. A baseline assessment of dietary intake among survivors will be done using a 3-day food diary approximately 1 year after diagnosis. The rationale for being that is to observe survivor's habitual dietary intake, when they are back to their normal life after completion of all conventional treatment. Survivors dietary intake assessment will be subsequently repeated at third and fifth year after diagnosis (Figure 1).

Study Participants

This study starts including breast cancer patients diagnosed and managed in the UMMC since February 2012 and will continue recruiting until February 2017. The participants will be followed up at six months, one, three and five years after the date of recruitment and this will continue until 2022. All newly diagnosed breast cancer patients in the UMMC breast clinic will be screened for eligibility. Only the eligible patients who give consent will be recruited. Figure 1 shows the detail information of our recruitment strategy.

Eligibility Criteria

Inclusion Criteria

All women who are newly diagnosed with primary breast cancer in University Malaya Medical Center (UMMC):

- Aged 18 years and above
- Diagnosed between February 2012 to December 2017
- Within 3 months of diagnosis
- TNM stage I- IV breast cancer.
- Malaysian
- Able to converse either in Malay, English, Mandarin, or Tamil.

Exclusion Criteria

- i. Patients with prior history of any other cancer.
- ii. Patients whose attending physician certifies them as unfit due to other prevailing medical condition
- iii. Bedridden at time of recruitment .

Ethics And Dissemination:

The study protocol and procedures were approved by the UMMC Ethical Committee, (MEC Number 896.150). We have obtained full permission from the European Organization for Research and Treatment of Cancer (EORTC) to use the quality of life questionnaires, EORTC QLQ-C30 and QLQ-BR23. Ethical approval had also been obtained from University Malaya Cancer Research Institute (MEC No:775.9) for collection of biospecimen. Eligible patients will be verbally informed and explained regarding the nature and the purpose of the study by the trained research personnel and given time to decide on their participation. Written informed consent will be obtained from study participants prior to their enrollment and all collected information will be treated as confidential. We intend to present the results of our cohort study via scientific publication (peer-reviewed) as well as presentation to stakeholders including the public, patients, clinicians and policymakers via appropriate avenue.

Measures:

Exposure Measures:

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3 The exposure of interests are demographic variables (e.g. age at diagnosis, ethnicity, age at marriage, age
4 at first child birth, age at last child birth), socioeconomic variables (income, highest attained-education
5 and occupation), anthropometric measurements (e.g. height, weight, waist hip circumference, percentage
6 of body fat), diet (habitual food intake), use of complementary and alternative medicine (CAM) (e.g.
7 used other type of treatment other than hospital treatment), physical activity, work related variables (type
8 of work, working hour), health related variables (e.g. physical condition, appetite), and psychosocial
9 variables (e.g. anxiety, depression) and biomarker (e.g. blood, tumor tissues).

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12 Data on the exposure of interest will be obtained through personal interview (face-to-face), food
13 diaries, anthropometric, and biological measurement. Details of which is described in Table 1.

14 15 **Outcome Measures:**

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18 Patients will be monitored through follow-up in the breast cancer outpatient clinics in UMMC.
19 Patients who are unable to attend clinics and those who are not scheduled for regular follow-up in
20 UMMC, will be contacted by phone.

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23 The primary outcome is overall survival. Data on mortality will be obtained from the hospitals' medical
24 records, as well as active follow-up through the next-of-kin of patients. In addition, we will regularly
25 update the vital status of patients through direct linkage with the National Registration Department
26 (NRD), Malaysia, which holds the death records in Malaysia.

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29 The cohort will be followed up with scheduled phone calls and clinic visits in a systematic way to update
30 patient's health status. Another outcome is quality of life (QoL). QoL will be measured based on response
31 of a quality of life questionnaires obtained from the European Organization for Research and Treatment
32 of Cancer (EORTC). The EORTC QLQ-C30 comprised 30 items that includes five functional scales
33 (physical, role, emotional, cognitive and social) and nine symptoms scale (fatigue, nausea and vomiting,
34 pain, dyspnea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) and Global health
35 status scale. On the other hand, the QLQ-BR23 is a more detailed questionnaire containing 23 items that
36 comprises 23 questions designed for quantifying the quality of life of breast cancer patients. It includes
37 five functional scales (body image, sexual functioning, sexual enjoyment, future perspective), and four
38 symptoms scale (systemic therapy side effect, breast symptom, arm symptom, upset by hair loss).
39 Information from the questionnaires will be scored accordingly. The raw score for each subscale will be
40 calculated and subsequently linear-transformed to 0 – 100 (standardized raw score) according to the
41 guidelines of EORTC scoring manual. A higher score for functional scale represents a high/healthy level
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of functioning. A high score for the global health status/QoL represents a high QoL. However a high score for a symptoms scale represents a high level of symptom that indicates a worst quality of life.

Tools used for measures:

i. Anthropometry:

Body mass index (BMI), body fat percentage and waist hip ratio (WHR) will be used as indicators of body fatness. World Health Organization (WHO) definitions and classifications will be used. Patients' nutritional status will be measured from BMI, body fat analysis (BFA), WHR and food diaries. BMI and BFA will be measured at baseline and a subsequent follow-up at half year, first year, third year and fifth year period. WHR will be measured only during baseline period. BMI and BFA, body fat percentages will be measured using a portable body composition analyzer (TANITA BC-418 Body Composition Analyzer, Tokyo, Japan). This equipment will calculate body fat ratio, body fat mass, fat free mass, estimated muscle mass and Basal Metabolic Rate using data derived by using Bioelectric impedance analysis (BIA). Hydration status, recent physical activity, consumption of food or beverages, temperature, menstrual status, and body position are among the factors that can affect the validity and precision of the measurements. For example, subjects should avoid alcohol for and vigorous exercise for 12 hours before testing, so that body fluids are not perturbed prior to the measurements. The measurements should be taken on subjects approximately three hours after eating, and within 30 minutes of voiding.

ii. Food Diary:

Habitual food intake will be assessed using a self-administered three-day food diary. A qualified trained dietitian will provide information and give instruction on how to complete the three-day dietary records. The food diary will be generalized to all ethnic groups (Malays, Chinese and Indians). A mini food album detailing (multiethnic) Malaysian food items will be provided for their guidance. Subjects will be reassessed at two-years, and four-years after initial dietary assessment.

iii. Questionnaire:

Questionnaires will be used to obtain detailed information on concurrent illness, work related factors, complementary and alternative medicine (CAM) use, physical activity, and QoL [23-25] (described in details in Table 1). Questionnaire for return to work self-efficacy scale (RTW-SE), readiness for return to work scale, and CAM use have undergone linguistic, content and face

validation. Physical activity will be measured using the Global Physical Activity Questionnaire (GPAQ). Presence of anxiety and depression will be assessed using the Hospital Anxiety and depression Score (HADS). To measure QoL, two module will be used; EORTC QLQ-C30 and EORTC QLQ-BR23, which has been translated and validated to the local languages. The validity and reproducibility of EORTC QLQ-C30, GPAQ, and HADS had been proven to be satisfactory [26-28].

Table 1: Measurement domains and data collection time points

Theme	Instruments	Baseline	6 Months	1 Year	3 Years	5 Years
Demographic and socioeconomic characteristics	- Socio-demographic -Social- Economy background (Questionnaire)	× ×	×			
Quality of Life	- European Organization for Research and Treatment of Cancer Core quality of Life questionnaire (EORTC QLQ-C30) - European Organization for Research and Treatment of Cancer Breast Cancer Quality of Life Questionnaire (QLQ-BR23)	× ×	× ×	× ×	× ×	× ×
Body weight and Nutrition	- Anthropometric measurement (BMI, WHR) - Food diary and mini food album	×	×	× ×	× ×	× ×
Physical Activity	- Global Physical Activity Questionnaire (GPAQ)	×	×	×	×	×
Complementary and alternative Medicine (CAM)	- CAM questionnaire	×	×	×	×	×
Psychosocial factors	- Hospital Anxiety and depression Score (HADS) & - Distress Thermometer (Questionnaire)	× ×	× ×	× ×	× ×	× ×
Work related factors	- Return to work self-efficacy scale (RTW-SE) - Readiness for return to work scale	× ×	× ×	× ×	× ×	× ×
Clinical, histological biological factors	- Clinical registry and Biobank (Blood, urine and tissues)	× ×	×	× × (only blood)	×	×

iv. Clinical registry:

There is already an established prospective breast cancer registry in UMMC [11], which include data on reproductive factors and family history; tumor characteristics i.e. size, grade, TNM stage, receptor status (estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2) and treatment details i.e. treatment modalities (surgery, radiotherapy, chemotherapy and hormonal therapy). We will regularly link the current study variables to the registry.

Data Collection Point**Baseline**

At the time of recruitment to the study, the following information will be recorded:

- Demographic factors and clinical data
- Information on the other illness/ co-morbidities
- Detailed information on
 - ✓ Quality of life
 - ✓ Psychosocial factors
 - ✓ Work related factors
 - ✓ Physical activity
 - ✓ Complementary and alternative medicine use and
- Biospecimen (blood, urine and tissues) will be preserved
- BMI, WHR and BFA measurement

Follow-up

the following information will be collected at half year, first year, third year and fifth year after diagnosis:

- Clinical data and information on concurrent illness
- Detailed information on
 - ✓ Quality of life
 - ✓ Psychosocial factors
 - ✓ Physical activity
 - ✓ Complementary and alternative medicine use
 - ✓ Work related factors
 - ✓ Food diaries (during 1st, 3rd and 5th year follow-up period) and

- BMI and body fat analysis (BFA) measurement

Figure 1 demonstrates the overall flow of the study .

Data Analysis

Statistical Analysis

The results of survivor's demographics and baseline outcome variables will be summarized using descriptive summary measures, expressed as mean or median for continuous variables and proportions for categorical variables. We will report model coefficient for continuous outcomes, odds ratio (OR) for binary outcomes, or hazards ratio (HR) for time to event outcomes, with the corresponding 95% confidence intervals, and associated *p*-values. To determine the quality of life among breast cancer patients at different stages of the illness we will use scores obtained from the EORTC QLQ-C30 and EORTC QLQ-BR23 instruments. A higher score represents a "better" level of functioning and global health status, or a "worse" level of symptoms. Median and other quartiles with 95% confidence interval (CI), will be obtained for all the domains of QoL index according to stage of breast cancer. The Anova test will be conducted to determine the QoL score for each domain, according to respective cancer stages and ethnicity, *P* value <0.05 will be considered to be statistically significant.

Important prognostic factors will be identified by fitting the Cox's proportional hazard model. Overall survival will be estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariable Cox regression analysis will be used to estimate the relative risk of all-cause mortality (hazard ratio) associated with the various prognostic factors that we are studying. We will also assess whether ethnicity modifies the association between various prognostic factors and overall survival, as well as QoL.

Statistical Power

We estimate that we will be able to recruit about 1000 women during the six years of enrolment i.e. 150-200 patients per year in UMMC. With reports showing Malaysia to have the highest prevalence of obesity in Asia [29], we hypothesize that change in body weight may explain most of the survival disparities associated with lifestyle. Previous studies in UMMC recorded a mean BMI of breast cancer patients at diagnosis as 23.8 kg/m² (SD 4.12) and that the overall five year survival is 75% [20, 21]. A Cox regression of the log hazard ratio on BMI of these women with a standard deviation of 4 kg/m² based

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3 on a sample of 1000 participating women achieves an output of 90% statistical power at a 5%
4 significance level to detect a regression coefficient of BMI (kg/m^2) equivalent to 0.0468. Recruitment of
5 even 750 patients, will be able to achieve 80% statistical power at 5% significance to detect a significant
6 difference.
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10 11 12 **Discussion**

13
14 Prognoses of breast cancer among Asian women vary considerably from Western women and may
15 attributed due to difference in lifestyle, socioeconomic profile, health believes, culture and genetic
16 backgrounds [10]. Previous studies in selected populations (Malaysian) suggested that ethnicity is an
17 independent prognostic factor of breast cancer survival [21]. Development of biomarkers for prognosis,
18 expanding biobank and furthermore outcome measures and quality of life measures among cancer
19 survivors are relatively scarce in Asia.
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25 To the best of our knowledge, this study is the first in a multiethnic Asian setting to determine the
26 association between socio-demographic and lifestyle factors on overall survival and Quality of Life (QoL)
27 in breast cancer survivors. Notably, previous cohort studies [11, 30] only conducted survival analysis
28 utilizing clinical data. Results from our study can provide imminent insights into association between
29 patient's nutrition, BMI, body composition, physical, mental and socioeconomic status, on their quality
30 of life and overall survival. We will also be able to assess the influence of ethnicity on these associations.
31 A major strength of this study will be that we are using well-validated and reliable tools (i.e. GPAQ and
32 portable TANITA) [31-33] to measure modifiable risk factors (i.e. physical activity, body composition).
33 This study will add evidence on the impact of body fatness and its changes on overall survival and quality
34 of life of Asian women following the diagnosis of breast cancer. In addition, there will be long-term
35 storage of patient's blood, serum, plasma, urine and tissues in the UMMC Biobank for future research.
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44 There are some limitations to the current study. It is expected that there will be some
45 ambiguity in assessing the overall improvement or decrement in quality of life of the survivors, as
46 perception varies from one individual to another. Nevertheless the validity and reproducibility of QoL
47 was satisfactory [27] and adopted from the European Organization for Research and Treatment of Cancer
48 (EORTC). Given that we have chosen to address a cohort comprising mostly of urban residents attending
49 a tertiary hospital, our findings may not necessarily reflect the overall situation of breast cancer survivors
50 in Malaysia. Another limitation is that we will be using a three-day food diary that depends on the
51 respondent's full co-operation. However, diet history will be taken from two weekdays and one weekend
52 and as such should reflect more valid estimates of patient's habitual dietary intake [34].
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On the basis of the cohort study proposed here, this knowledge will be important for developing an effective strategy for the improvement of the overall survival and quality of life of breast cancer patients in middle-income countries such as Malaysia, whereby resources for health care are limited. This study will enable relevant parties to address prognostic factors that affect survival and enable a thorough focus to be placed on differences among ethnicity. Hence, we hope results from our study will contribute to the advancement in evaluation and appraisal methods for assessment of prognostic factors in breast cancer. In the long run, we aim to improve the survival and quality of life following the diagnosis of breast cancer in Asian women.

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Members of MyBCC working group

Taib NA, Bhoo-Pathy N, Su TT, Majid HA, Nahar AM, Ng CG, Dahlui M, and Hussain S, from University of Malaya, and Cantwell M, and Murray L from Queen's University Belfast

Footnotes

Contributors

NAT, TI, NB, and TTS are the principal investigators who designed the study and drafted the manuscript. MD, LM, MHA, and AMN have made substantial contributions to the conception and design of the project; NCG, MC and SH have been involved in drafting the manuscript. TI and NB are in charge of the statistical analysis. All authors critically revised the manuscript for important intellectual contents and provided the approval of the final version to be published.

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Competing interest

We have no competing interests to declare.

Ethics approval

This protocol was approved by the local Ethics committee of UMMC in January 2012.

Provenance and peer review

Not commissioned; externally peer reviewed

Data sharing

Further information such as statistical examination can be obtained from the first author

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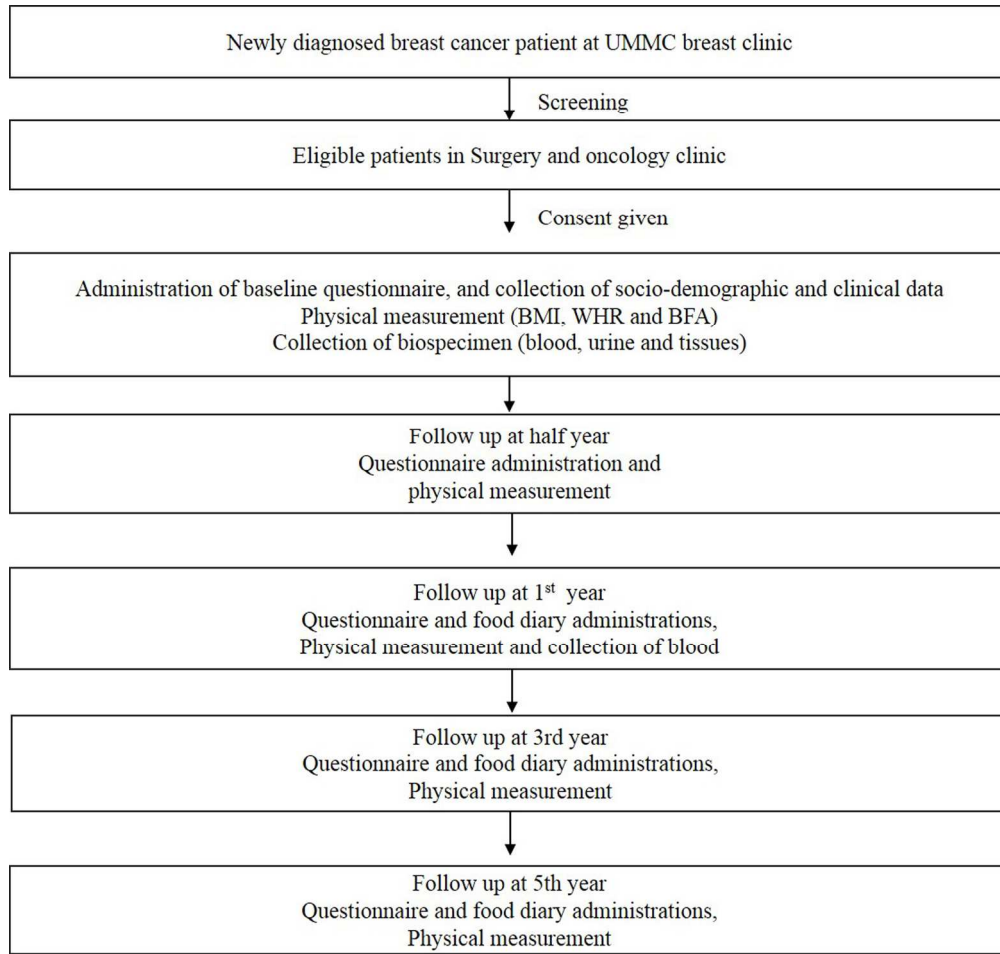


Figure 1. Flowchart of study recruitment process and overall study design
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