ORIGINAL ARTICLE

# The Contribution of Reproductive Factors and Family History towards Premenopausal Breast Cancer Risk in Kuala Lumpur, Malaysia

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**SUMMARY**

**Breast cancer is the most common cancer among Malaysian women. This study aimed to determine the reproductive for premenopausal breast cancer risk in Kuala Lumpur, Malaysia. A case-control study was conducted in 216 histopathologically confirmed cases of premenopausal breast cancer and 216 community-based controls that were matched by age within a 5-year period and ethnicity. The results of this study showed that premenopausal breast cancer risks were strongly related to parity, number of live births and family history of breast cancer. Premenopausal women with these known reproductive and family history risk factors should take extra measures to undergo appropriate screening method for early detection of breast cancer.**

**KEY WORDS:**
*Case-control studies; Risk factors; Reproductive; Family history; Premenopausal; Breast cancer*

## INTRODUCTION

Breast cancer is the most common cancer in women worldwide and second most common cancer overall [1]. In Malaysia, the National Cancer Registry (NCR) reported 3,525 new cases of breast cancer in 2006 giving an age standardised incidence rate (ASR) of 39.3 per 100,000 women [2]. Of these, 1526 cases were diagnosed before the age of 50 with an ASR of 14.9 per 100,000 women. Breast cancer has been one of the major health problems in Malaysia and become increasingly important public health concern [3].

Well-established reproductive factors for breast cancer are age at menarche and menopause [4], parity and age at first childbirth[5]. In addition, strong evidence exists for increased risk in individuals having a family history of breast cancer [6, 7]. Genetic factors, including the major susceptibility genes i.e. BRCA1 and BRCA2, may account for up to 10% of breast cancer cases in developed countries [8, 9], but their prevalence in the population is too low to explain much of international variation in risk. Different environmental factors might therefore be the cause of these variations in risk. As the breast tissue, hormones and hormone-receptor status varies at different stages of life, individual risk factors will have different effects accordingly. Breast cancer typically develops after menopause, but it is especially worrisome when it develops earlier. It seems to be more aggressive in younger and premenopausal women, while the underlying causes are largely unknown.

It is therefore important to learn the risk factors for premenopausal breast cancer to assist in screening and early detection measures in combating the disease. Over the past decade, several studies conducted by local researchers have focused on the possible role of reproductive factors and family history in relation to risk of breast cancer among Malaysian women. Risk factors of breast cancer have been investigated among women in Kuala Lumpur [10-13], women in Kelantan [14] and women in Sabah [15]. These assessed breast cancer cases without stratification for menopausal status and therefore produced inconsistent results. There was a need for local data on risk factors separately for premenopausal and postmenopausal breast cancer. Therefore, this study was done to determine the contribution of reproductive factors and family history for breast cancer among premenopausal women in Kuala Lumpur, Malaysia. Information gathered can hopefully be used to plan screening methods and to educate the public on early detection of the disease.

## MATERIALS AND METHODS

*Subjects*

This study was carried out between January 2006 and December 2007 in Kuala Lumpur, Malaysia as part of Genetics, Molecular and Proteomic Study of Primary Breast Cancer in Malaysia (IRPA 09-02-02-009 BTK/ER/37). The study received Medical Ethical Committee approval from Universiti Kebangsaan Malaysia Medical Centre (FF 166-

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2004). Subjects were confined to premenopausal women. Premenopause is defined as the phase before the permanent cessation of menses. Premenopausal women will still have normal or irregular menstrual period. Cases were women recruited from Kuala Lumpur Hospital and Universiti Kebangsaan Malaysia Medical Centre, which were the main referral hospitals for breast cancer cases in Kuala Lumpur. These cases were newly diagnosed with histologically confirmed malignant breast cancer between the study periods. Inclusion criteria for cases were premenopausal Malaysian women aged between 18 to 55 years, were not terminally ill and diagnosed with primary breast cancer. All breast cancer patients registered and diagnosed during the study period i.e. 674 cases were identified and screened for eligibility. Of these women, 263 did not meet the inclusion criteria with 198 were menopause women, 19 were non-Malaysian, 6 did not meet the age requirement, 37 were terminally ill and 3 with secondary breast cancer. From the remaining 411 (60.9%) eligible cases, 158 refused to take part with personal reasons and others agreed to participate in the study and provided informed consent. Then, 15 cases refused to answer the questions during interview using standard questionnaire to gather information on risk factors. Another 22 cases with many missing data were excluded. Finally, 216 cases were included in statistical analyses. Overall response rate for cases was 52.6% (216/411).

Community-based controls were recruited by poster advertisements as invitation tool to health screening programmes carried out at several residential areas around Kuala Lumpur during the same study period. They were matched by age ± 5 years and ethnicity using a ratio of 1:1. Exclusion criteria were menopause women, personal history of any types of cancer or previously diagnosed with other terminal disease. Of the 612 controls attended the health screening programme, 381 (62.3%) women meet the inclusion criteria and were eligible. Consent was obtained from 281 to participate in this study. The reasons for refusal were mainly lack of interest. Eighteen women gave incomplete information and they were excluded from analyses. Finally, after matching all cases with their controls, the remaining 47 controls were excluded making the overall response rate as 56.7% (216/381).

*Data Collection*

Data for this study was collected using face-to-face interview with a pilot tested questionnaire including questions about socio-demographic characteristics, medical history, reproductive factors, family history of breast cancer, lifestyle habits (use of hormones, smoking and alcohol consumption) and current weight and height to calculate body mass index. The interview was conducted by two trained-interviewers and the same interviewer interviewed all matched cases and control in every possible instance. All data were obtained up to the reference year i.e. the year before diagnosis for cases and the year before recruitment into the study for controls. The mean time interval between diagnosis and interview of cases was 1.8 months, and 92% (198/216) of cases were interviewed within 3 months of diagnosis. The mean time interval between interview of the index case and her matched control was 3.6 months. Of the 216 case-control pairs, 87% (188/216) were interviewed within 6 months of each other. An informed consent was obtained from all cases and controls beforehand.

*Statistical Analysis*

Descriptive characteristics were performed to characterize the study group and to examine case-control differences. The differences were assessed using chi-square ($\chi^2$) test for categorical variables and t-test for differences in means. Relationships between risk factors and breast cancer were determined using binary logistic regression to obtain odds ratios (ORs) and the 95% confidence interval (95%, CI) as estimates of relative risks. Tests for linear trend were performed on all ordinal and continuous variables using linear regression analysis producing p-trend values. The main outcome (dependent variable) was incident cases of breast cancer while independent variables were the reproductive variable and family history variable. Two sets of analyses were performed. In the first model, ORs were adjusted only for age. In the second model, multivariate analysis was applied using forced entry method to control for other factors. Models included adjustment for age (continuous) and other known in research literature risk factors and potential confounders that were selected a priori i.e. marital status, education level, working status, household income, age at menarche, parity, age at first childbirth, number of live birth, family history of breast cancer in first-degree relatives, history of breastfeeding, duration of breastfeeding, use of oral contraceptive pills (OCP), alcohol consumption and body mass index (BMI) as classified in Table II and Table III. All p-values are two sided and a p-value less than 0.05 is considered as statistically significant. Analyses were done using Statistical Package for Social Sciences (SPSS) for Windows version 15.0 (SPSS Inc., Chicago, IL).

## RESULTS

Table I summarizes the characteristics of study subjects by case and control group. The mean age at recruitment of the subjects was 42.6 ± 6.7 years for cases and 42.0 ± 6.6 years for controls (p=0.316). Cases and controls were similar in term of mean age and ethnicity as the result of matching done prior to statistical analysis. Both cases and controls were also similar for working status, household income, age at menarche, breast feeding duration, alcohol consumption, OCP use, weight, height and BMI. Compared with controls, cases were somewhat less educated, were more likely to be singles, widowed, or divorced. Cases also have less number of live births, older at first childbirth, more likely to have had a family history of breast cancer among their mother or sisters and to be most ever cigarette smoker as compared to their controls.

Multivariable adjustments to calculate the ORs with 95% CIs appeared to modify the relation between premenopausal breast cancer risks and reproductive variables as presented in Table II. The ORs were similar to those in simple analyses, which were adjusted for age indicating limited interaction between reproductive variables and other known factors. There is no evidence of lowered risk by having later age of menarche (p>0.05). However, strong protective effect from breast cancer risk was observed for being parous. Parous women in this study have 47% of reduction in risk for

**Table I: Selected characteristics of the study subjects**

| Variables | Cases (n=216) | | Controls (n=216) | | p-value [a] |
|---|---|---|---|---|---|
| Age at recruitment (years), mean (SD) [b] | 42.6 | (6.7) | 42.0 | (6.6) | 0.316 |
| Ethnicity, number (%) | | | | | |
| Malay | 117 | (54.2) | 117 | (54.2) | 1.000 |
| Chinese | 75 | (34.7) | 75 | (34.7) | |
| Indian | 24 | (11.1) | 24 | (11.1) | |
| Education level, number (%) | | | | | |
| No formal education | 5 | (2.3) | 11 | (5.1) | <0.0001 |
| Primary | 57 | (26.4) | 43 | (19.9) | |
| Secondary | 113 | (52.3) | 85 | (39.4) | |
| Tertiary | 41 | (19.0) | 77 | (35.6) | |
| Marital status, number (%) | | | | | |
| Never married | 26 | (12.0) | 15 | (6.9) | 0.002 |
| Married | 166 | (76.9) | 194 | (89.8) | |
| Widowed/ divorced | 24 | (11.1) | 7 | (3.2) | |
| Working status, number (%) | | | | | |
| Housewife | 97 | (44.9) | 82 | (38.0) | 0.143 |
| Employed | 119 | (55.1) | 134 | (62.0) | |
| Household income (RM), mean (SD) | 3 660 | (3 670) | 4 094 | (3 972) | 0.236 |
| Age at menarche (years), mean (SD) | 13.0 | (1.5) | 13.1 | (1.5) | 0.414 |
| Number of live births, mean (SD) | 2.5 | (1.8) | 3.0 | (1.8) | 0.002 |
| Age at first childbirth (years), mean (SD) [c] | 25.8 | (4.7) | 24.9 | (4.1) | 0.046 |
| Family history of breast cancer, number (%) [d] | 29 | (13.4) | 6 | (2.8) | <0.0001 |
| Breastfeeding (months), mean (SD) | 5.4 | (7.7) | 7.0 | (10.2) | 0.062 |
| OCP – ever, number (%) [e] | 67 | (31.0) | 66 | (30.6) | 0.917 |
| Alcohol – ever, number (%) [e] | 11 | (5.1) | 15 | (6.9) | 0.418 |
| Smoking – ever, number (%) [e] | 5 | (2.3) | 0 | (0) | 0.025 |
| Weight (kg), mean (SD) | 61.3 | (13.1) | 61.1 | (12.1) | 0.884 |
| Height (cm), mean (SD) | 155.1 | (6.0) | 155.4 | (5.2) | 0.612 |
| Body mass index (kg/m$^2$), mean (SD) | 25.5 | (5.4) | 25.3 | (4.9) | 0.725 |

[a] All p-values are univariate and were derived using the Student's t-test for continuous variables and the Chi-square test for categorical variables,
[b] SD, standard deviation,
[c] Among parous women,
[d] Among first degree relatives only,
[e] Regular consumption or use.

**Table II: Multivariate adjusted odds ratio and 95% confidence intervals for premenopausal breast cancer in relation to reproductive factors**

| Reproductive factors | Cases (n=216) | Controls (n=216) | OR[a] (95% CI) | OR[b] (95% CI) |
|---|---|---|---|---|
| Age at menarche | | | | |
| < 12 years | 81 | 75 | 1.00 | 1.00 |
| > 12 years | 135 | 141 | 0.84 (0.56 – 1.26) | 0.82 (0.52 – 1.30) |
| Parity | | | | |
| Nulliparous | 1.00 | 24 | 1.00 | 1.00 |
| Parous | 175 | 192 | 0.47 (0.26 – 0.83) | 0.53 (0.30 – 0.91) |
| Age at first childbirth | | | | |
| < 25 years | 72 | 95 | 1.00 | 1.00 |
| 25 – 29 years | 65 | 75 | 1.15 (0.73 – 1.80) | 1.27 (0.75 – 2.15) |
| ≥ 30 years | 38 | 22 | 2.29 (1.23 – 4.19) | 2.62 (0.89 – 6.43) |
| | | | p-trend = 0.010 | p-trend = 0.064 |
| Number of live birth | | | | |
| None | 43 | 24 | 1.00 | 1.00 |
| 1 – 2 | 67 | 51 | 0.71 (0.38 – 1.32) | 0.73 (0.39 – 1.36) |
| 3 – 4 | 75 | 98 | 0.40 (0.22 – 0.74) | 0.42 (0.23 – 0.76) |
| > 5 | 31 | 43 | 0.39 (0.19 – 0.78) | 0.40 (0.20 – 0.79) |
| | | | p-trend = 0.001 | p-trend = 0.043 |

OR, odds ratio; CI, confidence intervals; Logistic Regression, Method = Enter, Contrast = Simple
[a] Adjusted for age (continuous),
[b] Adjusted for age (continuous), marital status, education level, working status, household income, age at menarche, parity, age at first childbirth, number of live birth, family history of breast cancer in first-degree relatives, history of breastfeeding, duration of breastfeeding, use of oral contraceptive pills (OCP), alcohol consumption and body mass index (BMI),

**Table III. Multivariate adjusted odds ratio and 95% confidence intervals for premenopausal breast cancer in relation to family history**

| Family history | Cases (n=216) | Controls (n=216) | OR[a] (95% CI) | OR[b] (95% CI) |
|---|---|---|---|---|
| Breast cancer in any relatives c | | | | |
| No | 163 | 203 | 1.00 | 1.00 |
| Yes | 53 | 13 | 5.19 (2.75 – 9.82) | 4.81 (2.41 – 9.58) |
| Breast cancer in first-degree relatives d | | | | |
| No | 187 | 210 | 1.00 | 1.00 |
| Yes | 29 | 6 | 5.14 (2.21 – 11.93) | 5.45 (2.10 – 14.13) |

OR, odds ratio; CI, confidence intervals; Logistic Regression, Method = Enter, Contrast = Simple

[a] Adjusted for age (continuous),

[b] Adjusted for age (continuous), marital status, education level, working status, household income, age at menarche, parity, age at first childbirth, number of live birth, family history of breast cancer in first-degree relatives, history of breastfeeding, duration of breastfeeding, use of oral contraceptive pills (OCP), alcohol consumption and body mass index (BMI),

[c] Any relatives includes mother, daughter, sister, aunt, cousin, grandmother,

[d] First-degree relatives includes mother, daughter, sister,

premenopausal breast cancer when compared with nulliparous women (OR=0.53; 95% CI, 0.30-0.91). Nevertheless, no association was found in the current cohort between risks of premenopausal breast cancer with age at first childbirth after multivariate analysis (p>0.05). Compared to nulliparous premenopausal women, there was a trend for decreasing risk with higher number of live birth for one to two live births (OR=0.73; 95% CI, 0.39-1.36), three to four live births (OR=0.42; 95% CI, 0.23-0.76) and five or more live births (OR=0.40; 95% CI, 0.20-0.79) with p value for trend of 0.043.

Table III presents the study findings of multivariate adjusted ORs with 95% CIs for family history of breast cancer. A history of breast cancer in any relatives (mother, daughter, sister, aunt, cousin, grandmother) increases the risk of premenopausal breast cancer by 4.8 fold (95% CI, 2.41-9.85). Further analysis looking into first-degree relatives (mother, daughter, sister) increased the ORs of premenopausal breast cancer up to 5.4 fold (95% CI 2.10-14.13).

## DISCUSSION

This case-control study provides a description and analysis of reproductive risk factors of breast cancer as well as family history, which are non-modifiable breast cancer risk factors. The results showed that being parous reduces the risk of premenopausal breast cancer while having a positive family history of breast cancer strongly increases the risk. These findings are consistent with several studies for parity and number of live birth [16-20] and for family history of breast cancer [7, 21-22].

This study found a 47% reduction of risk by being parous for premenopausal breast cancer risk, a similar protective relationship to that found by The Japan Public Health Centre-based prospective study [16]. They found that being nulliparous increases the risk by 66% compared to parous women. The findings also agree with previous study from the Shanghai Breast Cancer Study which showed increase on risk of premenopausal breast cancer from being nulliparous with an OR of 3.3 [19]. The Women's CARE Study found that premenopausal Whites but not African-American were having increased risk of breast cancer for being nulliparous (OR=1.5) [17]. Parous women were found to have decreased risk of breast cancer with an OR of 0.36 among young twins (less than 50 years) in an international population-based study [18]. A study in New Zealand suggest that women aged 45 to 49 years who were parous have some reduced risk of breast cancer compared to nulliparous women (OR=0.58) [20]. Interestingly, a study among Pakistani women aged less than 45 years found that being parous actually increased their risk of developing breast cancer [23]. Kruk [24] and Gilliland *et al.* [25] did not find any associations between parity and premenopausal breast cancer risk. However, studies among premenopausal women in relation to parity are limited as several studies looked into all breast cancer cases without menopausal stratification [26-30]. A local study found that nulliparity increases the risk of breast cancer with an OR of 15.3. In general, nulliparity increases the lifetime incidence of breast cancer [8]. Russo *et al.* [31] discussed mechanisms that might be associated between parity and breast cancer. It involves breast cell differentiation during pregnancy and further exhibit different susceptibility to carcinogenesis. Plasma prolactin levels were suggested to have of association at least in part between parity and premenopausal breast cancer risk [32]. Recently, Lee *et al.* [33] suggest that parity protects BRCA1/2 mutation carriers who are in the high-risk group from developing breast cancer.

Age at first childbirth was previously shown to have independent protective effects for premenopausal breast cancer [16, 18, 19, 34]. Most of the findings consistently agree that first pregnancy at older age of more than 30 years is associated with an increased risk of premenopausal breast cancer. Ponten *et al.* [35] proposed a multistep process of carcinogenesis, which includes initiation, promotion, tumour and progression. Undifferentiated cells that have not undergone the maturation process may be initiated by carcinogenesis and after promotion give rise to a breast tumour several years later. The differentiation of breast cells that occurs during the third trimester of pregnancy makes them less sensitive to initiating agents. Unfortunately, the magnitude of increased premenopausal breast cancer risk demonstrated in reported studies were not found to be significant in this study after adjustment for various breast cancer risk contributing factors. A study from Singapore also found that there is no association with age at first childbirth and premenopausal breast cancer that might suggest that no significant association between this factor in low-incidence breast cancer regions [36].

In the present study, a significant inverse trend was seen with higher number of live birth and risk of premenopausal breast cancer (p-trend<0.05). Five or more live births exhibit 60% reduction of premenopausal breast cancer risk. This was consistent with a study of women aged 45 to 54 years with an OR of 0.50 to 0.62 but not significant for younger women [20]. Iwasaki *et al.* [16] also found that low parity among premenopausal women was significantly associated with an increased risk of breast cancer. In contrast, Gao *et al.* [19] did not find any association between number of live births and breast cancer risk among younger women that was consistent with previous local and Singapore studies [10, 11, 14, 36]. Study of Women's Health Across the Nation (SWAN) findings support a mechanism for number of live births and breast cancer that involves mammographic density among premenopausal women [37]. Mammographic density prior to menopause may be a surrogate for lifetime estrogens exposure and higher mammographic density is associated with an increased risk of breast cancer [38].

Young age at menarche has long been recognized as a risk factor for breast cancer, and the age at establishment of regular menstrual cycles has been found to be a risk factor independent of age at menarche, perhaps because regular menstruation might be associated with increased cumulative estrogen exposure [39]. In the current study, age at menarche was not found to be associated with premenopausal breast cancer risk. This finding was similar to other local studies [10, 11, 14]. However, early age at menarche for premenopausal women were found to have detrimental effect towards risk of breast cancer in studies at Japan [16], China [19], France [34], Poland [24] and United States [40]. Rapid adolescent growth might increase the risk of breast carcinoma development [40]. However, in a twin study there is no evidence for association between earlier first period or earlier first regular period and premenopausal breast cancer risk [18]. An interesting study that looked into length of menstrual cycle found short and long menstrual cycle lengths at ages 18-22 years were associated with reduced risk of premenopausal breast cancer [41]. The results agreed with the previous hypothesis that propose a protective effect against breast cancer by reduced exposure to ovulatory menstrual cycles.

This study revealed that premenopausal women with a history of breast cancer in any relatives or first-degree relatives had a significantly higher risk of breast cancer compared to those without a similar family history, which was consistent with previous studies [7]. Premenopausal women with a family history of breast cancer either in any relatives or first-degree relatives exhibit a five-fold excess risk (OR=4.81 for any relatives; OR=5.45 for first-degree relatives) compared to findings that shows only two-fold increase in risk [6, 7]. Both meta-analysis for 74 studies and collaborative re-analysis for 52 studies found that the risk ratios associated with a family history of breast cancer tended to be even greater among younger women compared to older women. However, most local studies failed to find any association between family history and breast cancer risk among Malaysian women [10-12]. Norsa'adah *et al.* [14] interestingly agrees with the current study by having a four-fold increase in risk among women with a family history of breast cancer.

Up to 10% of breast cancer in Western countries is due to genetic predisposition [8]. Breast cancer susceptibility is generally inherited as an autosomal dominant with limited penetrance. Much attention was given to hereditary breast cancer which accounts for 5% to 9% of all breast cancers [42]. It was estimated that the combination of BRCA1 and BRCA2 gene mutations was responsible for approximately 80% of the families with hereditary breast cancer [43, 44]. Lightenberg *et al.* [45] found a lower risk, which contributed 30% risk for patients with family history of germline mutations in BRCA1 and BRCA2. In Asia, Japanese women with a family history have a risk of 38% to 46% of mutation on BRCA1 and BRCA2 [46, 47]. Studies on prevalence of BRCA1 and BRCA 2 mutation in Malaysia are still ongoing [48].

The results of this study must be interpreted in the light of possible biases that case-control studies are subject to. A population sample rather than hospital-based cases would make the results more applicable. Since only a moderate response (52.6%) rate was achieved in this study, selection bias is possible. Incentives for the respondents can be considered in future to increase the response rate. Recall biases were also expected as regard to information gathered such as for age at menarche, age at first pregnancy and detailed family history of breast cancer. We found contradicting data reported by patients during interview compared to data written in their medical reports by medical team. Although it was rarely found in our data, when this occurs, we chose data collected from the face-to-face interview as it was judged more reliable after clarification with the patients. As for family history data, patients were more aware of their family member's disease compared to controls. Not spreading words about ones disease especially among family members is part of Asian cultures since there is still significant stigma in talking about cancer, which give problems in exploring sufficient data of their family history 49. Unknown family history especially for second and third degree relatives were considered as no family history of breast cancer. Data collected after breast cancer diagnosis using standard questionnaire were not free from response information bias, as cases would be more aware of their lifetime factors compared to controls. Moreover, the moderate response rate among both cases and controls might contribute to difference in characteristics among respondents and non-respondents, which were not looked into in this current study.

Strengths of this study were a large sample of cases and controls specifically among premenopausal women. This study was able to provide simultaneous description and analysis of several established reproductive factors for breast cancer as well as those probable and possible risk factors. In addition, the impact of having a family history of breast cancer was also studied. Dose-response relation over different levels of variable was examined in all analyses using continuous data. An adequate adjustment for exposure to a broad range of potential confounders relating to reproductive and family history of breast cancer was carried out. Restriction of cases with histoptahologic examination reports which confirms the status of disease added the strength of this study.

## CONCLUSION

In conclusion, significant reproductive factors that contribute towards premenopausal breast cancer risk found in this study were parity and number of life births. Being parous and having a large number of live births were established protective factors for breast cancer. Meanwhile, there were non-significant association for age at menarche and age at first childbirth with premenopausal breast cancer risk, although there were well-established factors presented in larger cohort studies. As for premenopausal women with a family history of breast cancer, the risk of getting the disease is higher than previous findings in Western countries. Therefore, studies on genetics of the disease in Malaysia are necessary in order to elucidate the real influence of having a positive family history among premenopausal women with breast cancer. It is recommended that premenopausal women with these known reproductive and family history risk factors take extra measures to undergo appropriate screening method for early detection of breast cancer, which includes breast-self examination, clinical examination and high-resolution ultrasound adjunct to annual mammograms.

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## REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005; 55: 74-108.
2. Zainal AO, Zainudin MA, Nor Saleha IT. 2008. Malaysian cancer statistics – data and figure peninsular Malaysia 2006. Kuala Lumpur: National Cancer Registry, Ministry of Health Malaysia, 2008.
3. Lim GC. Overview of cancer in Malaysia. Jpn J Clin Oncol. 2002; 32 Suppl: S37-42.
4. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev. 1993; 15: 36-47.
5. Lambe M, Hsieh C, Trichopoulos D, Ekbom A, Pavia M, Adami HO. Transient increase in the risk of breast cancer after giving birth. N Engl J Med. 1994; 331: 5-9.
6. Collaborative Group on Hormonal Factors in Breast Cancer. Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58, 209 women with breast cancer and 101,986 women without the disease. Lancet. 2001; 358: 1389-99.
7. Pharoah PD, Day NE, Duffy S, Easton DF, Ponder BA. Family history and the risk of breast cancer: a systematic review and meta-analysis. Int J Cancer. 1997; 71: 800-9.
8. McPherson K, Steel CM, Dixon JM. ABC of breast diseases. Breast cancer-epidemiology, risk factors, and genetics. BMJ. 2000; 321: 624-8.
9. Polyak K. Breast cancer: origins and evolution. J Clin Invest. 2007; 117: 3155-63.
10. Hejar AR, Chong FB, Rosnan H, Zailina H. Breast cancer and lifestyle risks among Chinese women in the Klang Valley in 2001. Med J Malaysia. 2004; 59: 226-32.
11. Kamarudin R, Shah SA, Hidayah N. Lifestyle factors and breast cancer: a case-control study in Kuala Lumpur, Malaysia. Asian Pac J Cancer Prev. 2006; 7: 51-4.
12. Rabeta MS, Shahar, S., Arshad, F., Ghazali, A.R., Normah, H., Rajab, N.F. Abdominal obesity increased breast cancer risk. Malays J Health Sciences. 2007; 5: 17-28.
13. Shahar S, Normah H, Fatimah A, Fadilah RN, Rohi GA, Amin I *et al*. Antioxidant intake and status, and oxidative stress in relation to breast cancer risk: a case-control study. Asian Pac J Cancer Prev. 2008; 9: 343-49.
14. Norsa'adah B, Rusli BN, Imran AK, Naing I, Winn T. Risk factors of breast cancer in women in Kelantan, Malaysia. Singapore Med J. 2005; 46: 698-705.
15. Leong BD, Chuah JA, Kumar VM, Yip CH. Breast cancer in Sabah, Malaysia: a two year prospective study. Asian Pac J Cancer Prev. 2007; 8: 525-9.
16. Iwasaki M, Otani T, Inoue M, Sasazuki S, Tsugane S. Role and impact of menstrual and reproductive factors on breast cancer risk in Japan. Eur J Cancer Prev. 2007; 16: 116-23.
17. Li CI, Littman AJ, White E. Relationship between age maximum height is attained, age at menarche, and age at first full-term birth and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2007; 16: 2144-9.
18. Swerdlow AJ, De Stavola BL, Floderus B, Holm NV, Kaprio J, Verkasalo PK, et al. Risk factors for breast cancer at young ages in twins: an international population-based study. J Natl Cancer Inst. 2002; 94: 1238-46.
19. Gao YT, Shu XO, Dai Q, Potter JD, Brinton LA, Wen W, *et al*. Association of menstrual and reproductive factors with breast cancer risk: results from the Shanghai Breast Cancer Study. Int J Cancer. 2000; 87: 295-300.
20. McCredie M, Paul C, Skegg DC, Williams S. Reproductive factors and breast cancer in New Zealand. Int J Cancer. 1998; 76: 182-8.
21. Reinier KS, Vacek PM, Geller BM. Risk factors for breast carcinoma in situ versus invasive breast cancer in a prospective study of pre- and post-menopausal women. Breast Cancer Res Treat. 2007; 103: 343-8.
22. Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, *et al*. Association of family history and other risk factors with breast cancer risk among Japanese premenopausal and postmenopausal women. Cancer Causes Control. 2001; 12: 349-58.
23. Gilani GM, Kamal S. Risk factors for breast cancer in Pakistani women aged less than 45 years. Ann Hum Biol. 2004; 31: 398-407.
24. Kruk J. Association of lifestyle and other risk factors with breast cancer according to menopausal status: a case-control study in the Region of Western Pomerania (Poland). Asian Pac J Cancer Prev. 2007; 8: 513-24.
25. Gilliland FD, Hunt WC, Baumgartner KB, Crumley D, Nicholson CS, Fetherolf J, et al. Reproductive risk factors for breast cancer in Hispanic and non-Hispanic white women: the New Mexico Women's Health Study. Am J Epidemiol. 1998; 148: 683-92.
26. Nemesure B, Wu SY, Hambleton IR, Leske MC, Hennis AJ. Risk factors for breast cancer in a black population-the Barbados National Cancer Study. Int J Cancer. 2009; 124:174-9.
27. Albrektsen G, Heuch I, Hansen S, Kvale G. Breast cancer risk by age at birth, time since birth and time intervals between births: exploring interaction effects. Br J Cancer. 2005; 92: 167-75.
28. Tamakoshi K, Yatsuya H, Wakai K, Suzki S, Nishio K, Lin Y, *et al*. Impact of menstrual and reproductive factors on breast cancer risk in Japan: results of the JACC study. Cancer Sci. 2005; 96: 57-62.
29. Yavari P, Mosavizadeh M, Sadrol-Hefazi B, Mehrabi Y. Reproductive characteristics and the risk of breast cancer--a case-control study in Iran. Asian Pac J Cancer Prev. 2005; 6: 370-5.
30. Rosner B, Colditz GA, Willett WC. Reproductive risk factors in a prospective study of breast cancer: the Nurses' Health Study. Am J Epidemiol. 1994; 139: 819-35.
31. Russo J, Moral R, Balogh GA, Mailo D, Russo IH. The protective role of pregnancy in breast cancer. Breast Cancer Res. 2005; 7: 131-42.
32. Eliassen AH, Tworoger SS, Hankinson SE. Reproductive factors and family history of breast cancer in relation to plasma prolactin levels in premenopausal and postmenopausal women. Int J Cancer. 2007; 120: 1536-41.
33. Lee E, Ma H, McKean-Cowdin R, Van Den Berg D, Bernstein L, Henderson BE, *et al*. Effect of reproductive factors and oral contraceptives on breast cancer risk in BRCA1/2 mutation carriers and noncarriers: results from a population-based study. Cancer Epidemiol Biomarkers Prev. 2008; 17: 3170-8.
34. Clavel-Chapelon F. Differential effects of reproductive factors on the risk of pre- and postmenopausal breast cancer. Results from a large cohort of French women. Br J Cancer. 2002; 86: 723-7.
35. Ponten J, Holmberg L, Trichopoulos D, Kallioniemi OP, Kvale G, Wallgren A, *et al*. Biology and natural history of breast cancer. Int J Cancer Suppl. 1990; 5: 5-21.
36. Ng EH, Gao F, Ji CY, Ho GH, Soo KC. Risk factors for breast carcinoma in Singaporean Chinese women: the role of central obesity. Cancer. 1997; 80: 725-31.
37. Butler LM, Gold EB, Greendale GA, Crandall CJ, Modugno F, Oestreicher N, *et al*. Menstrual and reproductive factors in relation to mammographic density: the Study of Women's Health Across the Nation (SWAN). Breast Cancer Res Treat. 2008; 112: 165-74.
38. Boyd NF, Lockwood GA, Martin LJ, Byng JW, Yaffe MJ, Tritchler DL. Mammographic density as a marker of susceptibility to breast cancer: a hypothesis. IARC Sci Publ. 2001; 154: 163-9.
39. Feigelson HS, Henderson BE. The epidemiology of breast cancer. 2nd edn. London UK: Martin Dunitz Ltd, 2001.

40. Berkey CS, Frazier AL, Gardner JD, Colditz GA. Adolescence and breast carcinoma risk. Cancer. 1999; 85: 2400-9.
41. Garland M, Hunter DJ, Colditz GA, Manson JE, Stampder MJ, Spiegelman D, et al. Menstrual cycle characteristics and history of ovulatory infertility in relation to breast cancer risk in a large cohort of US women. Am J Epidemiol. 1998; 147: 636-43.
42. Ford D, Easton DF. The genetics of breast and ovarian cancer. Br J Cancer. 1995; 72: 805-12.
43. Rebbeck TR, Couch FJ, Kant J, Calzone K, DeShano M, Peng Y, *et al*. Genetic heterogeneity in hereditary breast cancer: role of BRCA1 and BRCA2. Am J Hum Genet. 1996; 59:547-53.
44. Greene MH. Genetics of breast cancer. Mayo Clin Proc. 1997; 72: 54-65.
45. Ligtenberg MJ, Hogervorst FB, Willems HW, Arts PJ, Brink G, Hagerman S, *et al*. Characteristics of small breast and/or ovarian cancer families with germline mutations in BRCA1 and BRCA2. Br J Cancer. 1999; 79: 1475-8.
46. Sugano K, Nakamura S, Ando J, Takayama S, Kamata H, Sekiguchi I, *et al*. Cross-sectional analysis of germline BRCA1 and BRCA2 mutations in Japanese patients suspected to have hereditary breast/ovarian cancer. Cancer Sci. 2008; 99: 1967-76.
47. Ikeda N, Miyoshi Y, Yoneda K, Shiba E, Sekihara Y, Kinoshita M, *et al*. Frequency of BRCA1 and BRCA2 germline mutations in Japanese breast cancer families. Int J Cancer. 2001; 91: 83-8.
48. Thirthagiri E, Lee SY, Kang P, Lee DS, Toh GT, Selamat S, *et al*. Evaluation of BRCA1 and BRCA2 mutations and risk-prediction models in a typical Asian country (Malaysia) with a relatively low incidence of breast cancer. Breast Cancer Res. 2008; 10: R59.
49. Chieng W-S, Lee S-C. Establishing a cancer genetics programme in Asia – the Singapore experience. Hereditary Cancer in Clinical Practice 2006; 4: 126-35.