

A Pilot Study: Reassessing Young Breast Cancer Risk Factor in Mainland of Penang, Malaysia

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Abstract: ***Introduction:** There is no clear cut off point determining age in young breast cancer. Multiple studies have shown that breast cancer among women diagnosed before age of 40 is increasing in trend and have poorer survival rate. Incidence rate among Malaysian breast cancer from the age of 25 and below 40 is also showed increasing trend. This is a pilot study to ascertain the risk factors among young breast cancer in mainland of Penang state, Malaysia. **Method:** This is a retrospective study which includes young women diagnosed with breast cancer from 1st January 2015 until 31st December 2019, from HSJ cluster hospitals. Inclusion criteria are 40 years old and below at the age of diagnosis of breast cancer, female with complete sociodemographic data. **Result:** This study has shown that 17.07% of women with young breast cancer are age before 31 years old and most are age from 36 to 40 years old. Young age at menarche (12 years old and below), positive family history of breast cancer, use of oral contraceptive pill, breastfeeding history and pregnancy history (parity at least 1 and above) are strongly associated with increased risk of young breast cancer with P - value < 0.05. **Conclusion:** This is a small - scale study on young breast cancer patient. Larger population study will follow to confirm these findings and dwell further on other possible risk factors.*

Keywords: breast cancer, young breast cancer, risk factor, family history of breast cancer

1. Introduction

Young breast cancer currently being defined by age of 40 years old and below. However, until today, there is still no clear cut off point to determine the age of young breast cancer. In study by Carey et al, women diagnosed before age of 40 years old has shown to have poorer survival rate. Young breast cancer account for more than 40% of cancer at this age group. [1] In US Surveillance, Epidemiology and End Results (SEER) cancer statistic review from 2000 to 2005, 6.6% of breast cancer among American women were diagnosed before age of 40. [2] In a 30 - year review study by Rebecca et al., there is 2 - fold increasing in trend among young breast cancer patients to develop more advance stage breast cancer which is metastatic breast cancer. The number of cases went up almost 2.1% per year from 1976 to 2009. [3] In Malaysia, breast cancer has contributed to 19.0% of all newly diagnosed cancer from 2012 to 2016 regardless of gender, as compared to 17.7% from 2007 to 2011. Incidence rate among Malaysian has increased at the age of 25. In year 2012 to 2016, age - standardized rate (ASR) has also increased to 34.1 per 100, 000 population as compared to 31.1 per 100, 000 from 2007 to 2011. Hospital Seberang Jaya (HSJ) in Penang is the head of cluster hospitals, which include in Hospital Kepala Batas (HKB), Hospital Bukit Mertajam (HBM), and Hospital Sungai Bakap (HSB). HSJ covers most of the breast cancer cases in government facilities in mainland of Penang. This is the pilot study with aim to investigate the risk factors among young breast cancer in mainland of Penang state, Malaysia.

2. Method

A case - control retrospective study was conducted from 1st January 2015 until 31st December 2019 in HSJ cluster hospitals. Inclusion criteria are all 40 years old and below at

the age of diagnosis of breast cancer, female, complete socio-demographic data and histopathological confirmed breast cancer. Exclusion criteria are breast cancer diagnosed after age of 40 years old, incomplete data and patients with unspecified laterality of tumors. We compare women diagnosed with breast cancer age 40 years old and below (cases) during this period with control of same age range who came in for consultation and/or treated in this service with sonographic evidence of negative for breast lesions. Each case was compared with 1 control. Socio - demographic data (age, ethnics) and clinical characteristics (age of menarche, oral contraceptive use, family history of breast cancer, gravidity, parity, age at first pregnancy, history of breast feeding, duration of breast feeding) were collected from patients' medical record and breast cancer registry.

A total of 82 patients (41 cases and 41 controls) were recruited into this study. Women diagnosed with breast cancer at 40 years old and below (cases) are compared with women of same range of age who came for consultation and/or treated in these facilities with sonographic evidence of negative breast lesions. Sample size was calculated by using StatCalc from Centre for Disease Control and Prevention (CDC). Odd ratio of 10.11 is quoted from variable (family history of breast cancer) in study by Felix Essiben et. al. Two - sided confidence level is 95% with power of study 98%. Each case was opposed with 1 control. Minimum sample size obtained was 41 cases and 41 controls.

3. Statistical Analysis

Statistical analysis was done by using Statistical Product and Service Solutions (SPSS) version 24. Chi square test has been used to analyze the differences between cases and controls. The significance threshold was set at 0.05. Logistic regression was performed to eliminate confounders.

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4. Result

From this study, most of the patient age 36 - 40 years old (61%) follow by 31 - 35 years old 26.8 %. In view of Malaysia is a multiracial country, majority of the patient is Malay 85.4% followed by Chinese 12.2% and Indian 2.4%.

Table 1

Table 1: Socio - demographic characteristic of cases and controls in HSJ Cluster

Variable	Case (N = 41) %	Control (N = 41) %
Age		
16 – 20	0.0	12.2
21 – 25	2.4	17.1
26 – 30	9.8	14.6
31 – 35	26.8	26.8
36 – 40	61.0	29.3
Ethnicity		
Malay	85.4	68.3
Chinese	12.2	14.6
Indian	2.4	17.1

We compare our patient data with non – malignancy patient's data. We found that oral contraceptive pills (OCP) usage, early age of menarche and primary family history of breast cancer that has *p value* <0.05 is the risk factor for breast cancer similar as normal breast cancer patient risk factor. However, full term malignancy, breastfeeding and breastfeeding duration does not protect patients from breast cancer as previous study with *p value* <0.05. **Table 2.**

Table 2: Exogenous hormonal, reproductive factor and menarche and their association with young breast cancer

Variable	Case		Control		P – value
	N	%	N	%	
OCP use					
No	12	29.3	35	85.4	0.000
Yes	29	70.7	6	14.6	
Full term pregnancy					
Nulliparous	5	12.20	18	43.9	0.003
Yes	36	87.80	23	56.1	
Breastfeeding					
Never	10	24.4	20	48.8	0.038
Ever	31	75.6	21	51.2	
Breastfeeding duration					
< 12 months	2	6.5	10	47.6	0.002
12 months and above	29	93.5	11	52.4	
Age of menarche					
≤ 12 years old	28	68.3	7	17.1	0.026
>12 years old	13	31.7	34	82.9	
Primary family history of breast cancer					
No	27	65.9	39	95.1	0.002
Yes	14	34.1	2	4.9	

5. Discussion

Age group/median

In our study, most of the patient's ages were from 36 to 40 years old, which accounts for 61.0%. It shows higher in comparison with a cohort study from FUSCC which is 57.115% but slightly lower than SEER cohort study which is 65.15%. The second most age group affected by young breast cancer are age from 31 to 35 years old which is 26.8%.

There is 26.18% of women at this age group in SEER cohort and 28.24% of women at this age group in FUSCC cohort. [2] [5] Age after 30 is a common age group for presentation of young breast cancer. Both our study and FUSCC cohort show a relatively younger age of presentations, with 12.2% and 14.61% of women diagnosed with young breast cancer before age of 31. Both studies show approximately 1.5 times higher than SEER cohort, which is 8.67% of women presented at this age group.

6. Estrogen Exposure

Menarche

In a cohort study by Rebecca Ritte et al, it shows a strong inverse correlation between age of menarche and breast cancer. There are 30.97% (ER+PR+), 37.73% (ER - PR -) and 32.46% (combining data of ER - PR - and ER+PR+) women attained menarche at 12 years old and younger among breast cancer patients. [6] In our study, there are 68.29% of women attained menarche at this age group and it is approximately 2 - fold increase in percentage as compared to cohort study. In another study by Collaborative Group on Hormonal Factors in Breast Cancer involving 117 epidemiological studies, data has shown that risk increase by 5% with each year younger at menarche. In another study, risk is 2.2 times higher among attain menarche at age of 10 or 11 as compared to those attain menarche at 12 years old and elder. [7] The earlier onset of ovulatory cycle has led to younger age of menarche and this has increased the period of exposure to estrogen. The exposure to estrogen has increased the risk of onset of breast cancer in women. In our study, women with younger menarche age in case group is 41.2% higher than in control group. There is significant correlation between young breast cancer and early menarche age with P - value of 0.026.

Pregnancy

In a meta - analytical study, breast cancer risk with each full - term pregnancy reduces by 3%. [10] The propose mechanism is that pregnancy led to full cell differentiation in the gland of breast cancer and reduce the risk of carcinogenesis. [9] Our study has shown a different result 87.80% of women in our study are pregnant before and 66.67% of them have their first pregnancy before age of 25. Our data has shown a totally different data and pregnancy is strongly associated as a risk of young breast cancer. The P - value is 0.003 and is similar with study conducted by Felix Essiben et al. with P - value of <0.001. [11] Hence, pregnancy may be a risk factor in increasing the risk of young breast cancer but a protective factor in reducing risk of breast cancer in older age group.

OCP

A study by Morch LS et. al shown that breast cancer risk is higher among women ever use contraceptive than women never use contraceptive before. There is approximately 1 extra breast cancer for every 7680 women using hormonal contraception for 1 year. [12] In another study by Collaborative Group on Hormonal Factors in Breast Cancer, it concluded that there is increase in relative risk of having breast cancer diagnosed among women using combined oral contraceptives. The risk is reduced after oral contraceptives are stopped for more than 10 years. [13] However, there are

few cohort studies showing that neither current nor past long-term usage of oral contraception are associated with increased risk of breast cancer. [14] [15] There are 68.29% of young breast cancer women in our study ever use oral contraceptive. It is approximately 1.7 times higher as compared to another study in Jordan by Sanaa et. al which shows 39.01% of breast cancer of all age group ever use oral contraceptive and this study show a strong correlation between oral contraception and breast cancer risk. [16] In our study, P-value is less than 0.001 and is the lowest among all variables to show that there is significant correlation between usage of OCP and young breast cancer. Further study narrowing down to association between young breast cancer risk and oral contraception should be done because there is controversy seen among studies of breast cancer in all age groups.

Breast feeding

Breast feeding has been a protective effect against breast cancer. In an Icelandic cohort study by Tryggvadottir et al., the women ever lactating are associated with decreased risk of developing breast cancer as compared to women who have never breastfed. [17] The protective effect is better observed in another analysis data of 47 epidemiological studies. This study estimates 4.7% risk reduction in developing breast cancer with every 12 months of breastfeeding. [18] Multiple studies have shown that breastfeeding in particular is significant inversely associated with risk of hormonal-receptor negative breast cancer which is more common to seen in young age.^{15, 16} However, in study by Islami et al. find out that there is no significant association between breastfeeding and risk of hormonal-receptor positive breast cancer. [16] In our study, P value between breastfeeding and young breast cancer is 0.038 which shows that breastfeeding is a risk factor strongly associated with increased risk of young breast cancer. A similar correlation has been found in study by Felix Essiben et al. [11] The longer the duration of breastfeeding (at least 12 months) has been associated with higher risk of young breast cancer with P-value of 0.002. Hence, we concluded breastfeeding is not a protective factor in young breast cancer.

Family history of breast cancer

Multiple studies have shown a strong correlation of family history of breast cancer with breast cancer risk. There is about 12.9% to 18.77% of women affected by breast cancer having affected first degree relative (mother, daughter or sister). [19, 20, 21] In an analysis data of 52 epidemiologic studies, the breast cancer risk associated with family history is significantly increased with the number of first degree relative with breast cancer. [20] A similar trend of presentation is observed in a statistic by American Cancer society. 24 out of 100 women will get breast cancer if she has at least 1 first degree relative with breast cancer and 36 out of 100 women will get breast cancer if she has at least 2 first degree relative with breast cancer. [22, 23] In our study, 31.71% of women with young breast cancer have primary family history of breast cancer and it is at least 1.6 times higher than studies mentioned above. Young breast cancer has a more significant correlation with primary family history of breast cancer as compared with breast cancers of all age group. P-value is 0.002 and young breast cancer is

significantly correlated with positive family history of breast cancer.

7. Limitations of Study

This is a retrospective hospital-based study with a small number of cases only can be recruited even though 5 years study had been conducted. A large populations study should be conducted in multiple centers in order to ascertain the risk factors among young breast cancer.

8. Conclusion

This is a small-scale (a pilot study) hospital-based study on young breast cancer patient. The result showed different risk factors applied to young breast cancer in comparison to older patients. Hence, larger population study should be performed to confirm these findings and dwell further on other possible risk factors such as environmental hazard and lifestyle.

9. Declaration

8.1 Ethical Approval

This study uses available data of patient in respective hospital. Hospital ethical committee has reviewed this study and has approved the study. No ethical committee references number available.

8.2 Consent for publication

Not applicable in this study

8.3 Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available due data confidentiality protection reason are available from the corresponding author on reasonable request.

8.4 Competing Interests and Funding

There is no competing interest in this study and it is self-funding by the authors and co-authors.

8.5 Author's contribution

Authors and co-authors contributing in this study by designing the study, data collection and analysis and manuscript preparation.

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