

INTERRELATIONSHIP OF CLINICOPATHOLOGICAL FEATURES OF BREAST CANCER AMONG DIFFERENT ETHNIC GROUPS

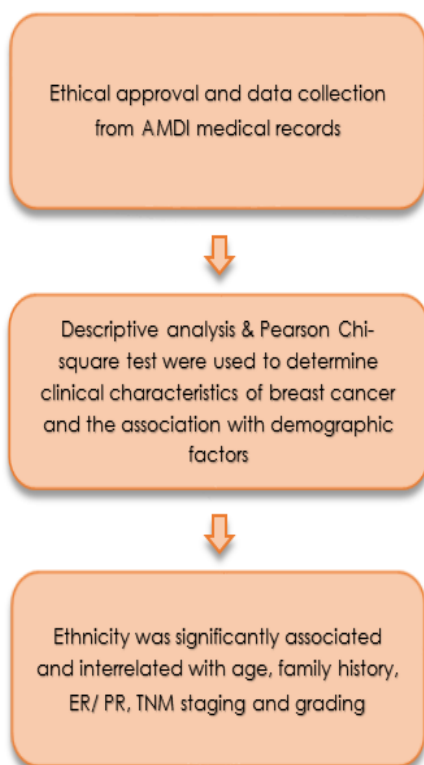
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Article history
Received
13 March 2016
Received in revised form
10 July 2016
Accepted
15 July 2016

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Graphical Abstract



Abstract

Breast cancer is a heterogeneous disease that can be classified using a variety of clinical and pathological features. In Malaysia, breast cancer remains the most prevalence malignancy among women which vary substantially by racial/ethnic group. A pilot study was conducted to determine clinical characteristics of breast cancer (BrCa) and the association with demographic factors from a set of data retrieved from Advanced Medical and Dental Institute (AMDI), Universiti Sains Malaysia (n = 236). In this study, 55.1% of the patients were Malay followed by Chinese (33.9%) and Indian (11.0%). By using Pearson Chi-Square test, it was reported that ethnicity was significantly associated with age at diagnosis (p = 0.001) and family history (p = 0.034). In addition, interrelationships (p value < 0.05) existed between: (1) ethnics with age at diagnosis (2) ER with PR, TNM staging and grading (3) PR with tumor grading. In summary, interrelationships status of BrCa clinicopathological features can be used to better understand BrCa in predicting prognosis for the patients.

Keywords: Breast cancer, demographic factors, clinicopathological features, race/ ethnicity

Abstrak

Kanser payudara adalah penyakit yang diklasifikasikan dengan pelbagai ciri klinikal dan patologi. Di Malaysia, kanser payudara kekal sebagai malignan yang secara lazimnya wujud di kalangan wanita berdasarkan kumpulan etnik yang berbeza. Kajian rintis telah dijalankan untuk menentukan ciri-ciri klinikal kanser payudara dan kaitannya dengan faktor demografi daripada data yang diperolehi dari Institut Perubatan dan Pergigian Termaju (IPPT), Universiti Sains Malaysia (n = 236). Dalam kajian ini, 55.1% pesakit adalah berketurunan Melayu, diikuti kaum Cina (33.9%) dan India (11.0%). Dengan menggunakan ujian *Pearson Chi-Square*, kaum tertentu didapati mempunyai kaitan yang signifikan dengan umur pada diagnosis (p = 0.001) dan sejarah keluarga (p = 0.034). Di samping itu, hubungkait (p < 0.05) wujud antara: (1) kaum dengan usia semasa diagnosis (2) ER dengan PR, tahap dan kelas TNM (3) PR dengan kelas tumor. Secara ringkas, status hubungkait antara ciri klinikal patologi kanser payudara boleh digunakan untuk lebih memahami kanser berkenaan dalam meramal prognosis terhadap pesakit.

Kata kunci: kanser payudara, faktor demografi, ciri klinikal patologi, kaum

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1.0 INTRODUCTION

Breast cancer has become as one of the most common cancer deaths among women these days. The International Agency for Research on Cancer [1] in 2012 has reported that 1.7 million women were diagnosed with breast cancer with 522,000 deaths. There was a sharp rise in previous five years where more than 20% increase in breast cancer incidence with 14% mortality [2].

Changes in lifestyle and due to the aging population have led cancer as the main cause of death for the past decades. The incidence rate of breast cancer has increased by 6.8% with the major risk factors detected were early menarche, late menopause, late full-term pregnancy (FTP) and low numbers of FTP [1].

In Malaysia, records from Malaysian Oncological Society have proven that breast cancer was the main cancer among Malaysian women [3].

Prognosis and survival rate of breast cancer vary greatly in different race/ ethnic. Iqbal *et al.* [4] reported significant differences in diagnosis of stage 1 breast cancer and risk of death in eight different racial/ ethnic groups. Asian women had the highest chance of getting stage 1 breast cancer and lower risk of dying compared with Caucasian women [4].

Management and prognosis of breast cancer depend on diverse pathological factors such as histological type, cancer stage, lymph node status, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor-2 (HER-2) expression status [5]. Thus the objective of this study was to determine the interrelationship of clinicopathological features of breast cancer patients among different ethnic groups.

2.0 METHODOLOGY

2.1 Study Population

The study was a cross-sectional retrospective study which comprises of a total of 236 breast cancer cases. The data was retrieved from the databank of Advanced Medical and Dental Institute (AMDII), Universiti Sains Malaysia from the year 2004 to 2012 where only breast cancer cases were prospectively evaluated. Information was obtained based on demographic and clinicopathologic features.

2.2 Instruments

Data from the positively diagnosed breast cancer patients were included with all relevant information. Demographic and clinicopathologic data including TNM staging, histopathology grading, tumor size and tumor receptor (ER, PR and HER2) were extracted from the medical records. Ethical clearance from the institutional ethical committee was obtained with the reference number: USMKK/PPP/JEPeM [256.4.(2.1)].

2.3 Statistical Analysis

Descriptive analysis was performed to analyze the mean and standard deviation (SD) for the continuous data. For categorical variables, Pearson Chi-square test or Fisher's Exact test was used to assess the association between different ethnic groups and age of diagnosis, family history, TNM staging, histopathology grading, estrogen receptor (ER) and progesterone receptor (PR); with percentages of categorical variables were also been calculated.

A *p*-value of < 0.05 were considered to be statistically significant. All statistical analyses were performed using PASW® Statistics Software (V22).

3.0 RESULTS AND DISCUSSION

3.1 Demographic Profiles

A total of 236 cases were recorded from the year 2004 to 2012 in AMDI USM. Various demographic profiles were presented in Table 1. Most of the study subjects were Malays (55.1%) followed by Chinese and Indian with 33.9% and 11.0% respectively. Racial disparities in incidence may be associated with lifestyle, reproductive factors and dietary intake. According to Abdullah *et al.* [6], Malays recorded the lowest 5-year survival rate of 45.1% compared to Chinese (49.1%) and Indian (54.2%).

The mean age reported in this study was 52.57 (± 10.54) years. This finding was consistent with the previous studies in Malaysia [6, 7, 8]. The youngest age at diagnosis was 22 years while the oldest was at the age of 89 years. Yip *et al.* [9] postulated that the younger age of breast cancer onset was due to the younger demographic age of Malaysian women (median age of 26.1 years) compared with Caucasian women (median age of 39.8 years in United Kingdom).

According to Zhou and Recht [10], young age group at diagnosis was considered as patients with the age younger than 40 years old. Few studies have shown that young breast cancer women developed more ER negative, higher histological grade and more triple negative subtype, thus suggesting poor prognosis of young breast cancer cases [11].

For histopathology grading, 63.1% were diagnosed as grade 1 and 2 while 36.9% were diagnosed as grade 3. 67.3% of the patients were presented at early stage (stage 1 and 2) and 32.6% came at later stage (stage 3 and 4). Factors that influenced the stage at presentation could be due to different ethnicity, education level, socio-economic status, access to treatment centers, strong belief in traditional medicine, negative perception of the disease, fear and denial of the disease [9, 12].

Patients exhibited biologically different tumors depending on the presence of estrogen and progesterone receptor as hormone sensitivity. In this study, estrogen receptor positive tumors were 58.9%,

which is comparable with other studies ranging from 48.2-57.4% [7]. 51.7% of the study population exhibited Her-2 positive cancers. Her-2 overexpressed tumors were likely to have high tumor grade and associated with the estrogen receptor expression [13, 14].

Tumor-expressed proteins (ER/PR and Her2) played a crucial role in determining breast cancer treatment. Forty-seven out of 236 cases (16.1%) was triple negative breast cancer (ER/PR-, Her2-), which known in contributing to poor prognosis of the disease and worst overall survival [15]. Most triple negative cases were connected with young age of diagnosis and high grade of tumor [9].

Table 1 Demographic profiles (n = 236)

		Frequency (%)
Age [mean (\pm SD) = 52.57 (\pm 10.543) yrs]	\leq 40 years	28 (11.9)
	41 – 55 years	129 (54.7)
	\geq 55 years	79 (33.4)
Ethnic	Malay	130 (55.1)
	Chinese	80 (33.9)
	Indian	26 (11.0)
Gender	Female	234 (99.2)
	Male	2 (0.8)
Marital Status	Yes	227 (96.2)
	No	9 (3.8)
Co-Morbid	Diabetes	5 (2.1)
	Hypertension	52 (22.0)
Histopathology	Grade 1	43 (18.2)
	Grade 2	106 (44.9)
	Grade 3	87 (36.9)
Estrogen Receptor (ER)	Positive	139 (58.9)
	Negative	97 (41.1)
Progesterone Receptor (PR)	Positive	131 (55.5)
	Negative	105 (44.5)
Tumor Receptor (HER2)	Positive	122 (51.7)
	Negative	114 (48.3)
Vascular Involvement	Yes	64 (27.1)
	No	172 (72.9)

N Staging	N0	133 (56.3)
	N1	84 (35.6)
	N2	15 (6.4)
	N3	4 (1.7)
M Staging	M0	224 (94.9)
	M1	12 (5.1)
Tumor Subtype	ER/PR+, HER2-	77 (32.6)
	ER/PR+, HER2+	74 (31.4)
	ER/PR-, HER2-	47 (16.1)
	ER/PR-, HER2+	47 (19.9)

3.2 Interrelationship of Clinicopathological Factors

Table 2 showed the interrelationships of different clinicopathological factors in breast cancer. Significant interrelationships (p -value $<$ 0.05) existed between: (1) ethnics with age at diagnosis (2) ER with PR, TNM staging and grading (3) PR with tumor grading.

A study by Warner *et al.* [16] has explained that factors such as stage at diagnosis, tumor characteristics and BMI were significantly contributed to the difference of ethnicity, where it was not consistent with our findings. However, a study by Chlebowski *et al.* [17] has a similar result to our study where their findings have also shown a statistically significant between ethnicity and age of diagnosis.

Estrogen receptor (ER) was found to be significantly interrelated with PR, TNM staging and grading. The finding was consistent with other studies by Ch'ng *et al.* [7] and Yip *et al.* [18] where ER status was demonstrated to be significantly interrelated with cancer stage, grade, age and race. The studies indicated that ER negative status had higher tumor grade and larger size. It was otherwise mentioned that ER positive tumor was prone to be in grade 1 cancers compared with grade 3 cancers. In addition, Malay women have a higher risk of ER negative tumors compared with Chinese women [18].

Zong *et al.* [19] stated that progesterone receptor was significantly associated with a higher tumor grade (p -value $<$ 0.05). This was consistent with our study where the results obtained also indicated progesterone receptor was significantly associated with tumor grading (p -value $<$ 0.001). Furthermore, Pichon *et al.* [20] also mentioned similar results in their study where they proved that progesterone receptor has significant interrelation between tumor grading (p -value $<$ 0.05). In contradiction, a study by Gupta *et al.* [21] illustrated that no significant associated existed between those tumor grading with progesterone receptor.

3.3 Association of Race/ Ethnicity with Clinicopathological Factors

A distribution of ethnicity and clinicopathological factors was illustrated in table 3. The three major ethnic groups were found to be significantly associated with age at diagnosis and family history (p -value < 0.05).

15.4% of Indian patients were diagnosed at very early age (≤ 40 years of age) followed by Malays (13.8%) and Chinese (7.5%). Few studies demonstrated a worse prognosis for patients younger than 35 years old [11, 22]. The present study identified a significant association (p -value < 0.001) between ethnic groups and age at diagnosis.

Different age at menarche, age at first birth, age at menopause, weight, parity and menopausal hormone therapy may influence the onset of breast cancer in certain ethnic groups [17].

For the incidence of breast cancer with family history, Malays exhibited the highest cases (89.2%). Patients with a family history have a significantly higher risk of getting breast cancer compared to those without family history. Several genetic factors have the potential to influence different breast cancer characteristics in different ethnic groups, found to be significantly associated in this study.

Table 2: Interrelationship between Clinicopathological Factors

	Age at diagnosis	Lymph node	Tumor Size	TNM Staging	ER	PR	Grading
Ethnics	< 0.001*	0.180	0.112	0.385	0.677	0.585	0.204
Age at Diagnosis		0.143	0.933	0.235	0.984	0.631	0.234
TNM Staging					0.038*	0.137	0.759
ER						< 0.001*	0.001*
PR							< 0.001*

* p -value < 0.05 level of significant.

Table 3: Association of Race/ Ethnicity with Clinicopathological Factors

(n=236)	Race/ Ethnicity			Total	t statistics ^a	p-value
	Malay (%)	Chinese (%)	Indian (%)			
Age at Diagnosis (years)						
≤ 40	18 (13.8)	6 (7.5)	4 (15.4)	28		
41 – 55	81 (62.4)	32 (40.0)	16 (61.5)	129	19.838	0.001*
≥ 55	31 (23.8)	42 (52.5)	6 (23.1)	79		
Family History						
Yes	116 (89.2)	61 (76.3)	23 (88.5)	200	6.767	0.034*
No	14 (10.8)	19 (23.8)	3 (11.5)	36		
TNM Staging						
Early Stage	86 (66.2)	58 (72.5)	19 (73.1)	163	1.153	0.562
Late Stage	44 (33.8)	22 (27.5)	7 (26.9)	73		
Histopathology Grading						
Grade 1	21 (16.2)	13 (16.3)	9 (34.6)	43		
Grade 2	58 (44.6)	37 (46.3)	11 (42.3)	106	5.931	0.204
Grade 3	51 (39.2)	30 (37.5)	6 (23.1)	87		

Estrogen Receptor (ER)						
Negative	55 (42.3)	30 (37.5)	12 (46.2)	97	0.781	0.677
Positive	75 (57.7)	50 (62.5)	14 (53.8)	139		
Progesterone Receptor (PR)						
Negative	57 (43.8)	34 (42.5)	14 (53.8)	105	1.072	0.585
Positive	73 (56.2)	46 (57.5)	12 (46.2)	131		

* p-value < 0.05 level of significant.

° Pearson Chi Square

4.0 CONCLUSION

In summary, demographic and clinicopathologic features could be used as prognostic and predictive factors for breast cancer patients. Interrelationship and association status of the features are crucial to better understand the disease in predicting prognosis for the patients. In this study, we found that ethnicity was significantly associated with age at diagnosis and family history. Significant interrelationship can also be observed between: (1) ethnics with age at diagnosis (2) ER with PR, TNM staging and grading (3) PR with tumor grading.

Acknowledgement

The authors gratefully thank the staff from Record Unit of AMDI and those who directly or indirectly involved in this study. The study was supported by Incentive Grant from Universiti Sains Malaysia (USM).

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