Effect of Ethnic Differences on Breast Cancer Presentation and Prognosis in Singapore

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Abstract

This manuscript examines the impact of ethnic differences on breast cancer presentation and prognosis among Malay, Chinese, and Indian women in Singapore. Data from the Singapore Cancer Registry and the Joint Breast Cancer Registry reveal significant ethnic differences in age-standardized incidence rates, median age at diagnosis, and screening uptake. Notably, Malay women present with breast cancer at a younger age and exhibit poorer survival rates, despite lower incidence rates. The study also explores the prevalence and outcomes of Triple Negative Breast Cancer (TNBC) across these ethnic groups, identifying variations in incidence and prognosis. Factors such as lifestyle, obesity, breastfeeding practices, socioeconomic status, and genetic predispositions are considered as potential contributors to these disparities. The findings highlight the need for targeted interventions to improve outcomes for ethnic minorities, emphasizing the complexity of breast cancer disparities in Singapore.

Keywords: Breast cancer, Cancer disparities, Ethnic differences, Singapore Cancer Registry, Triple Negative Breast Cancer (TNBC).

Introduction

Breast cancer is the leading cancer among Singaporean women, accounting for 20% of all female cancers, with an age-adjusted standardized rate (ASR) for mortality of 15.5 per 100,000. Across Southeast Asia, Singapore has the highest incidence rate of breast cancer (Ng et al., 2020). While the mortality rate has decreased, the incidence rate has rapidly increased for women over 50 years old.

In Malaysia and Singapore, multi-ethnic nations comprising 3 major ethnic groups, namely Malays, Chinese, and Indians, age-standardized incidence rates of breast cancer differ substantially. The rate is highest among the Chinese, followed by the Indians and the Malays. Despite having implemented a national screening program in 2002 and having government-funded medical schemes such as MediSave, attempts at creating equal access to services have not resulted in equal uptake or results across various ethnic groups. Whilst Malay women have the lowest incidence of breast cancer, there is

evidence of a poorer prognosis compared to other ethnic groups, whereby they show a younger peak age for breast cancer presentation, the worst stage of cancer during presentation, and the poorest survival rate (Abdullah and Mohamed, 2021). Compared to the Chinese, Malay ethnicity is associated with a significantly higher risk of all-cause mortality, independent of age, stage, tumor characteristics, and treatment. Whether the stage of diagnosis, tumor grade, treatment, or tumor biology are at the core of the poorer prognosis, however, remains unclear (Bhoo-Pathy et al., 2015).

Breast cancer is a heterogeneous disease that can be classified into different molecular subtypes with varying clinical outcomes. Triple-negative breast cancer (TNBC), defined as tumours negative for estrogen (ER), progesterone (PR), and human epidermal growth factor receptor (HER)-2, accounts for 10% to 15% of all breast cancers (Tang et al., 2019). While not the most common in Asia, TNBC is known to be more aggressive, having a greater likelihood of early metastasis and recurrence, and is, overall, associated with poor prognosis (Dent et al., 2007). Variation in the incidences of TNBC in different ethnic groups has been reported in Malaysia, where the incidence was higher in Malays than in Chinese and other ethnicities (Tak et al., 2012). Reasons for these ethnic differences in the incidence of breast cancer and, specifically, TNBC *are multifactorial and are caused due to a combination of biological and* non-biological factors. Overall, this study aims to explore the ethnic differences in the presentation and prognosis of breast cancer overall, focusing on TNBC in Singapore, and how variations in biological and non-biological risk factors contribute to these differences.

Methods

A retrospective review was performed on breast cancer patients treated in Singapore by analysing patient data published in the Singapore Cancer Registry 50TH Monograph and the Joint Breast Cancer Registry Annual Report 2022. The Singapore Cancer Registry's Monograph included anonymised data on tumours diagnosed in Singapore from 1968 till 2017. The annual report by the Joint Breast Cancer Registry included 28,692 patients diagnosed from 1960 to 2019 in tertiary hospital clusters. In addition, TNBC data at SGH, comprising 289 patients, was analysed, and other local studies based in South-east Asia were included as well. Statistical analysis was performed for the SGH data using SPSS software. A p-value of <0.05 was considered statistically significant.

Results

Breast Cancer Incidence and Patient Profile

Over the past 50 years, the age-standardised incidence rates (ASIR) of invasive breast cancer have increased consistently in all three ethnic groups; however, there are differences in the ASIR between them. In the period of 2013-2017, Chinese had the highest ASIR per 100,000 population (70.8), followed by Indians (65.8) and Malays (65.6). Consequently, in this period, the relative risk was the highest for Chinese (ref).

Additionally, the median age at diagnosis differs, whereby Malay patients are diagnosed at a much younger age (51.3 years) as compared to Chinese patients (53.9 years) and Indian patients (54.4 years). It was also noted that among the

Malay patients, 84% of the cases were detected clinically, while only 16% of the cases were detected radiologically. This differs from the Indian and Chinese patients, who had lower percentages of cases clinically detected (77% and 76%, respectively) (ref). This suggests differing screening uptake among the ethnic groups, whereby it was previously reported that Malays had the lowest mammography uptake as compared to others.

Table 1. Incidence, Relative Risk, and Mortality (per 100,000 population) in 2013-2017 by ethnicity as per Singapore Cancer Registry 50TH Anniversary Monograph.

	Total	Chinese	Malay	Indian
Incidence				
Number	10824	8668	1137	718
CIR (Crude Incidence Rate)	109.0	116.8	86.8	83.1
ASIR (Age-standardised Incidence Rate)	69.8	70.8	65.6	65.8
Relative Risk and 95% CI		1.00	0.93 (0.89-0.97 95% CI)	0.91 (0.81-1.04 95% CI)
Mortality				
Number	2180	1638	339	157
CMR (Crude Mortality Rate)	21.9	22.1	25.9	18.2
ASMR (Age-standardised Mortality Rate)	13.0	12.0	19.1	14.5

Breast Cancer Survival and Mortality Rates
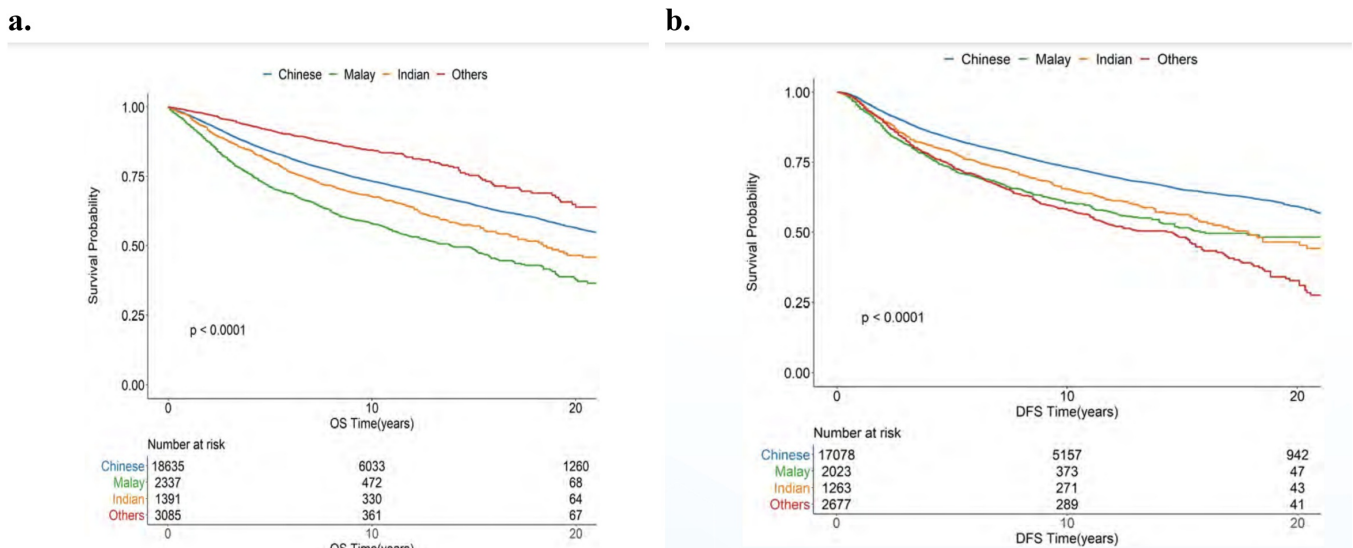
a.

b.

Figure 1. Overall survival (a) and disease-free survival (b) by ethnicity as per Joint Breast Cancer Registry 2022.

Overall survival (OS) and disease-free survival (DFS) varied between the three ethnic groups. Malays had the lowest

overall survival compared to Chinese and Indians. In addition, at 10 years, Malays had the lowest disease-free survival; however, at 20 years, Indians had the lowest disease-free survival, lower than Malays. Although the ASIR was the lowest for Malays, the ASMR (Age Standardised Mortality Rate) for Malays has been consistently higher than that for the other two ethnic groups since 1983. In the period 2013 – 2017, the ASMR per 100,000 population was the highest for Malays (19.1), followed by Indians (14.5), and lastly, Chinese (12.0) (ref).

Table 2. Tumour characteristics and Treatment by ethnicity as per Joint Breast Cancer Registry 2022 Report.

	Chinese	Malay	Indians
Median Age at Diagnosis (years)	53.9	51.3	54.4
Type of Presentation (%)			
Clinical	76	84	77
Radiological	24	16	23
Tumour Histological Subtype (%)			
Luminal A	61	56	57
Luminal B	18	19	16
HER 2+ve	10	13	10
Basal	11	11	18
Tumour Grade (%)			
Grade 1	15	9	12
Grade 2	41	35	42
Grade 3	44	56	46
TNM Staging (%)			
DCIS/LCIS	13	7	7
Stage 1	29	16	22
Stage 2	36	35	39
Stage 3	15	27	22
Stage 4	8	15	11
Type of Surgery (%)			
BCS	27	28	30
Mastectomy	62	63	60
No surgery	11	9	10
Chemotherapy Given (%)	66	76	64

Breast Cancer Tumour Characteristics

In terms of histological subtype of breast cancer, Luminal A is the most common across all ethnicities, present in 61% of Chinese, 56% of Malay, and 57% of Indians. Malay patients have a higher rate of Luminal B (19%) and HER 2+ve subtype (13%) as compared to others. The Basal subtype is more common in Indian patients (18%) than in other ethnic groups (both at 11%).

Among all three ethnic groups, Malays have a higher rate of Grade 3 tumors (56%) and the lowest rate of grade 1 tumors (9%). Furthermore, Malays have a higher percentage of advanced stage tumors, including stage 3 and 4 (27% and 15%), as compared to Indians (22% and 11%) and Chinese (15% and 8%). Pre-invasive cancers such as DCIS/LCIS were present at a higher rate in Chinese (13%).

According to a local study based in South-East Asia, it was found that a higher percentage of Malay women (17%) had distant metastasis compared to Chinese and Indian women (9% both). In addition, Malay women had a significantly increased risk of axillary lymph node metastasis compared to Chinese women (Bhoopathy et al., 2012).

Triple Negative Breast Cancer (TNBC)

In a similar manner, it was found in a retrospective review that the prevalence of TNBC varies among the different ethnic groups in Singapore, with prevalence highest in Indians (14.5%), followed by Malays (9.1%) and Chinese (7.5%) women. The median age at diagnosis for TNBC was lowest for Malays and Indians (50 years) as compared to Chinese women (56 years). Moreover, no major variations were found in TNBC tumour characteristics such as grade, stage, and nodal involvement among the ethnic groups.

Chinese women had a higher 5-year recurrence-free survival compared to Indian and Malay women, who showed similar 5-year recurrence-free survival. However, evidence of the association between ethnicity and survival in TNBC patients is conflicting in the literature, whereby another local study in South-east Asia noted that ethnic variations did not have an impact on OS and DFS (Alcantara et al., 2017). Analysis of in-house TNBC patient data at Singapore General Hospital indicated that Indians had a worse prognosis, with lower OS compared to Chinese (and no significant difference with Malays). Based on the same patient data, the correlation between ethnicity and DFS was not statistically significant.
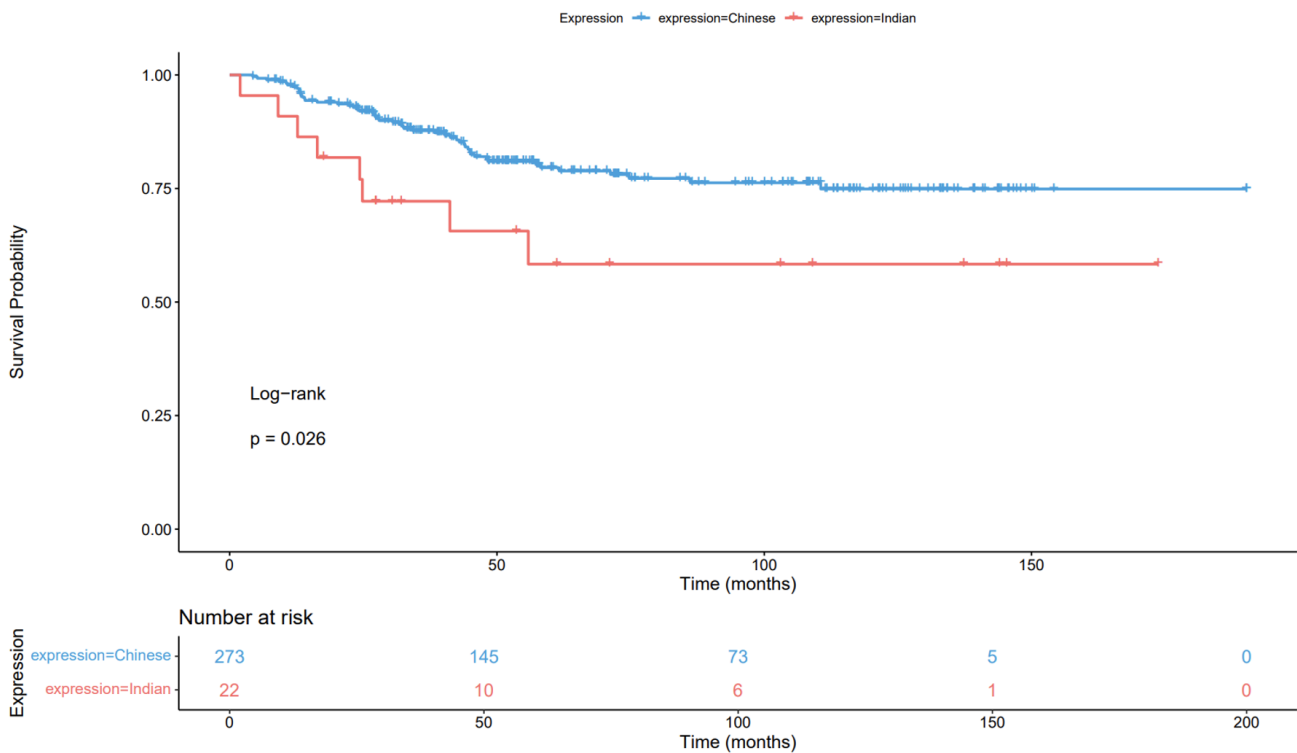
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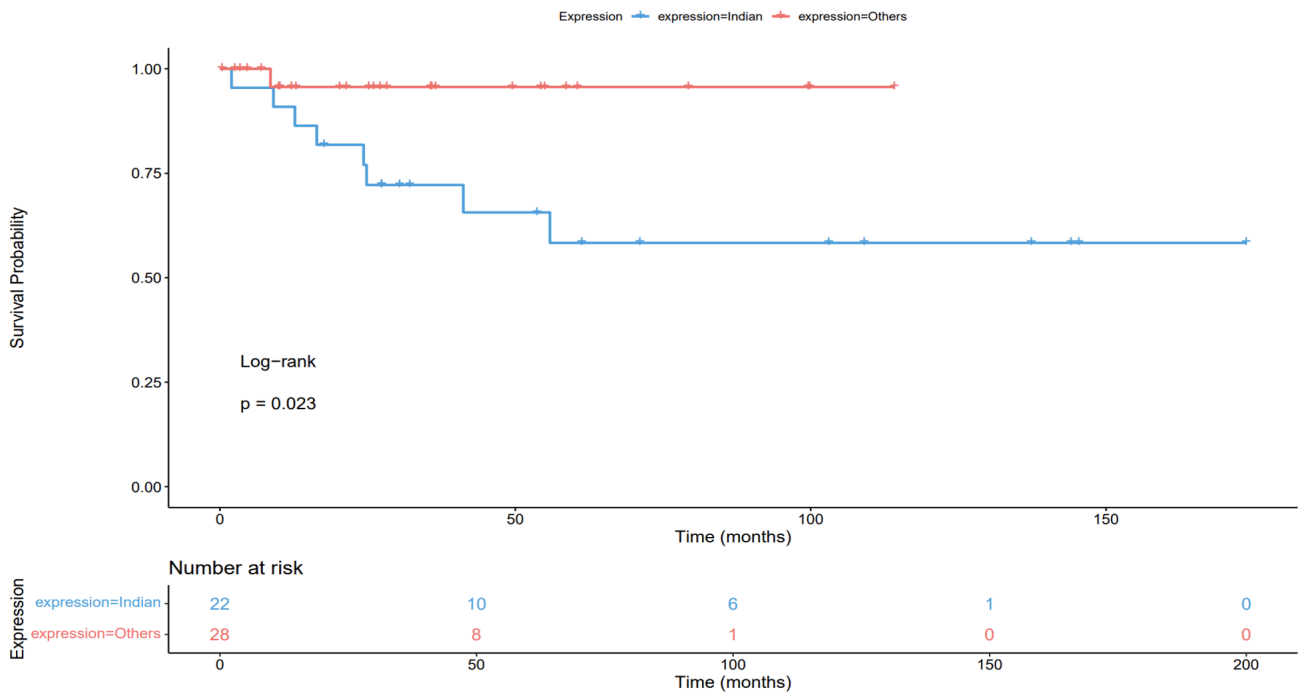
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Figure 2. Overall Survival between (a) Indians vs Others and (b) Indians vs Chinese (SGH TNBC patient data.

Discussion

Ethnic differences in lifestyle factors

Dietary Patterns

Dietary practices undeniably play a role in risk and prognosis. Unfortunately, effects of dietary habits on breast cancer presentation and prognosis have been understudied in Singapore, but the literature is far more available among various ethnic women in Malaysia (Abdullah and Mohamed, 2021). Undoubtedly, the different ethnic groups have preferential choices for cooking styles or ingredients.

For example, Malays and Indians have a greater tendency to utilize various spices such as turmeric or curcumin in their diet. Curcumin has been shown to have notable antitumor effects by regulating signalling cellular pathways in cultured breast cancer cells, inhibiting the proliferation of breast cancer cell lines such as T47D and MCF7, and inducing cell cycle arrest, and decreasing the expression of CDC25 and CDC2 proteins while increasing expression of P21 proteins (ref). As such, a correlation may exist between diets involving curcumin and lower risks of breast cancer among Malay and Indian women compared to Chinese women.

In a nutrient-wide association study, it was reported that a high intake of fiber and fruits was associated with a lower breast cancer risk (23). It was found that the total consumption of vegetables and fruits differs, whereby the Malays have the highest consumption, followed by the Chinese and the Indians (24), and this may influence breast cancer risk in these ethnic groups.

In Malaysia, among the three ethnic groups, binge drinking was recorded to be highest in the Indians (54%), followed by the Chinese at 39% and the Malays at 8% (25). The Malay women, who are Muslims, do not consume alcohol as it is forbidden in Islam. Some Chinese women consume alcohol on social occasions, and some Indian women in the estates consume illicit alcohol (26). Frequent and higher consumption of alcohol are risk factors for breast cancer, as shown in a study among premenopausal women in Japan (27). Due to the differences in alcohol consumption among the ethnic groups, breast cancer risk and incidence may also differ.

Obesity

Obesity is more common in Malay and Indian women, whereas the Chinese have the lowest body mass index [29,30]. Obesity has been linked to late stage at presentation of breast cancer as well as substandard diagnostic work-up [31]. In addition, body weight and weight gain after the diagnosis of breast cancer have also been implicated in the prognosis of breast cancer [32], which might explain some of the excess mortality among Malay and Indian women (Bhoo-pathy et al. 2012).

Obesity has been associated with an increased risk of developing BC and inferior survival in nonmetastatic, but not metastatic, BC (Yap, 2023). A meta-analysis found that obesity predicted modestly worse DFS and OS in all subtypes. Excessive estradiol production in the adipose tissue of individuals with obesity, insulin resistance with hyperinsulinemia, and altered adipokines with higher leptin and inflammation have been implicated in mediating a pro-tumorigenic

environment and predicting poor prognosis. Obesity may promote an immunosuppressive tumour microenvironment (TME) with M2 macrophages; loss of the beneficial effect from high stromal tumour-infiltrating lymphocytes (TILs) was also observed in patients with overweight receiving neoadjuvant chemotherapy for TNBC (ref). Comorbidities associated with obesity can increase the risk of non-BC deaths and affect the tolerability of cancer treatments. As such, ethnic groups with worse cancer survival outcomes are often the groups for whom obesity and related comorbidities are more prevalent.

Breastfeeding and Parity

Breastfeeding practices have been found to vary among the ethnic groups, whereby in the first 6 months, breastfeeding was practised by 52.5% of Malay women, 35.8% of Indian women, and 15.6% of Chinese women (Abdullah and Mohamed, 2021). In addition, a higher percentage of Malay women have longer durations of breastfeeding as compared to Chinese women. There is an association between breastfeeding and a decreased risk of the triple-negative BC phenotype, where a longer duration of breastfeeding leads to a significantly lower risk of TNBC (Shinde et al., 2010). It has been proposed that this is due to the failure of an expanded progenitor cell population in breast tissue to undergo differentiation and apoptosis with a shorter duration of breastfeeding, leading to an increased risk of carcinogenesis.

Parity differs between the ethnicities, with Malay women having higher fertility rates as compared to Chinese women (Abdullah and Mohamed, 2021). The risk for the TNBC phenotype increases by 12% with each birth, and in women with more than 3 children, the risk of this phenotype is 1.53 times more than that for nulliparous women (Shinde et al., 2010).

Socio-economic Status

Despite equal access to health care in Singapore, mammography uptake is lowest among women of Malay ethnicity, with only 28.9% reporting having attended mammography within the last 2 years in 2019, compared to their Chinese and Indian counterparts at 40.1% and 41.0%, respectively (Goh et al. 2022). Barriers continue to persist amongst Malay women in presentation and prognosis due to many factors such as misinformation on breast cancer, perceived negative outcomes from mammography, and perceived costs of treatment. Notably, all these factors are closely related to the socio-economic status of the ethnic groups.

In our population, the Chinese have the highest household income and are most likely to receive tertiary education, whereas the Malays have the lowest income and education status, and the Indians fall in between. Education levels have been found to be associated with poor health literacy (Ng et al., 2020). In Singapore, particularly among older Malay women, awareness and understanding surrounding breast cancer have been persistently low for over two decades and have hindered early presentation (Ng et al., 2020). The lack as well as inaccurate knowledge of cancer is prevalent in all three ethnicities, even in younger patients with professional degrees.

Cultural and Religious Beliefs

Data on breast cancer screening behaviour and its determinants specific to the Malay community is lacking. In 2018, a focus group of 27 English-speaking Malay women in Singapore elucidated that traditions, beliefs (religious, fatalistic,

cultural, and intergenerational), such as Islamic values that prohibit the revealing of the 'aurat' (intimate body parts), and spirituality influence the decision to screen for breast cancer (Shaw et al. 2018). Individuals holding a neutral perception towards modesty concerns in appearance, which is a core value of the Islamic faith, were most likely to attend screening compared to those that agreed with it.

Specific insights about the influence of religious beliefs on screening in the Malay community are often underpowered and inconclusive. For instance, Straughan and Seow found fatalism, a belief that some health issues are beyond human control, to be associated with mammography uptake in a survey among predominantly Chinese respondents (84.3%). The same authors also reported that Malay women were less fatalistic in a separate study, therefore leaving the relationship of fatalism and mammography uptake in this community inconclusive.

Ethnic differences in genetic factors

There is increasing evidence that germline genetics can influence somatic gene alterations or expression, as well as modulate the tumour or immune microenvironment. Although the precise mechanisms remain elusive, this may account for the varying distribution of different breast cancer subtypes across ethnicities (Yap, 2023).

According to previous genetic research, Chinese women had the highest incidence of BRCA1 and 2 mutations at 63.1%, followed by Malay women at 23.1% and Indian women at 11.8%. Among the Chinese women, there was an equal proportion of BRCA1 and 2 mutations. There were more BRCA2 mutations among the Malays. These mutations led to early onset breast cancer (age ≤40 years). A total of 27 deleterious mutations were detected (14 in BRCA1 and 13 in BRCA2), and 47 variants of uncertain clinical significance were identified (16 in BRCA1 and 31 in BRCA2). This study may significantly contribute to the current statistical evidence on the incidence of breast cancer by ethnicity (Abdullah and Mohamed, 2021). The reason for a higher proportion of BRCA2 mutations over BRCA1 mutations is not known, but this may reflect selection bias, genetic drift, or a possible genetic or environmental factor modifying the penetrance of BRCA1 or BRCA2 among Malays (Thirthagiri et al., 2008).

Differences in pharmacokinetics have previously been observed in Chinese, Malaysian, and Indian women treated with doxorubicin (Ma, Hui, & Mok, 2010). Polymorphic variants of the PXR*1B haplotype clusters have been linked to reduced activity of the pregnane X receptor and its downstream target enzymes, CYP3A4 and ABCB1/MDR1, which resulted in lower clearance of doxorubicin. Individuals carrying variants of the multidrug-resistance gene (ABCB1) and the CBR1 D1 gene experienced an increased clearance of doxorubicin and reduced peak plasma levels of doxorubicinol. Contrastingly, SNPs in SLC22A16, which are seen more frequently in Chinese women, are associated with increased AUC of doxorubicin and doxorubicinol concentrations. Certain treatments may therefore be more effective in one ethnic group than the other, particularly within Chinese women (BhooPathy et al., 2012).

Conclusion

In this study, it is evident that there are distinct ethnic differences in the presentation, biology, and prognosis, specifically

among TNBC patients in Singapore. Despite having a lower ASIR for breast cancer, Malay women were more likely to be diagnosed at a younger age and had a worse prognosis, with a higher ASMR and a lower overall survival. Malay women tend to have advanced-stage, high-grade tumours or HER2 overexpression even when other contributing factors are considered. Breast cancer was more frequently detected clinically in Malay women, which is reflected in the lower screening uptake in this group. Ethnic differences were seen in TNBC patients, where Indians and Malay women presented earlier and had higher disease recurrence rates than Chinese. While evidence on the effect of ethnicity on OS and DFS in TNBC patients is conflicting, analysis of TNBC patients at SGH indicated that Indians had a worse prognosis, with a lower OS than others (Fig 1).

The reasons underlying this effect of ethnicity on breast cancer presentation and prognosis in Singapore are multifactorial and complex. A variety of lifestyle factors, including dietary patterns, obesity, and breastfeeding, have been shown to contribute to driving this disparity in the risk and prognosis of breast cancer patients. Ethnic variations in tumour biology and mutations lead to a greater likelihood of an early onset and a more unfavourable breast cancer phenotype. Delayed presentation can be explained by cultural/religious factors and socio-economic factors such as poor literacy and financial concerns; religious issues surrounding modesty deter Malay women from undergoing screening and hence, delayed presentation. Overall, this study highlights the importance of understanding ethnic differences in the presentation and prognosis of breast cancer. The findings of this study also underscore the need for targeted interventions and ensure equity in clinical trial participation to improve the outcomes of breast cancer patients, particularly those from ethnic minorities.

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