

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

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Abstract

Background: Breast cancer is a significant health issue in Singapore, where it is the leading cancer among women. Triple-negative breast cancer (TNBC), accounting for 10% to 15% of all breast cancers, is known to be aggressive and associated with poor prognosis. In a multi-ethnic nation such as Singapore, variations in incidences and prognosis of breast cancer and TNBC among Malays, Chinese and Indians have been found previously. This study aims to explore the ethnic differences in the presentation and prognosis of breast cancer, focusing on TNBC in Singapore and evaluate how variations in risk factors contribute to these differences.

Method: A retrospective study on breast cancer patients from 1960 to 2019 was conducted, using data from the Singapore Cancer Registry (SCR) 50th Monograph and the Joint Breast Cancer Registry (JBCR) Annual Report 2022. The independent variable chosen was ethnicity, whereby it was divided into 'Indian', 'Malay', and 'Chinese'. The following dependent variables were considered: incidence, relative risk, median age at diagnosis, mortality, survival and tumour characteristics. In addition, survival analysis of 289 TNBC patients at Singapore General Hospital (SGH) was conducted.

Results: Despite having a lower ASIR, Malay had the lowest overall survival and highest ASMR than Chinese and Indians. Malays were diagnosed at a younger age (51.3 years), had the highest rate of grade 3 (56%), and advanced stage tumours (42%). Among TNBC patients in SGH, Indians were found to have lower OS compared to Malays and the Chinese.

Conclusion: Distinct ethnic differences in the presentation, biology, and prognosis of breast cancer patients in Singapore have been reported, with the Malay population predominantly experiencing poorer prognosis. Factors such as lifestyle, obesity, 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.

Introduction

Breast cancer is the leading cancer among Singaporean women. It accounts for 20% of all cancers among females and

has an age-adjusted standardized rate (ASR) for mortality of 15.5 per 100,000 (Ng et al., 2020). Across Southeast Asia, Singapore has the highest incidence rate of breast cancer. 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 three 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 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 has been associated with a significantly higher risk of all-cause mortality, independent of age, stage, tumour characteristics and treatment. Whether the stage of diagnosis, tumour grade, treatment, or tumour biology is at the core of 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 oestrogen (ER), progesterone (PR) and human epidermal growth factor receptor (HER)-2, account for 10% to 15% of all breast cancers (Tang et al., 2019). While not the most common in Asia, TNBC has been 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 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 such as lifestyle, obesity and socio-economic status.

With rising prevalence of breast cancer, it is imperative to understand the difference seen among different ethnicities in order to guide targeted interventions to improve outcomes. However, literature regarding the association between ethnicity and breast cancer in Singapore is limited, especially in contrast to the extensive research conducted on European populations. Therefore, the aim of this study is to explore the ethnic differences in the presentation and prognosis of breast cancer, focusing on TNBC, in Singapore and how variations in biological and non-biological risk factors contribute to these differences.

Methods

Data Sources

A retrospective review was performed on breast cancer patients treated in Singapore by conducting a secondary analysis using the Singapore Cancer Registry 50th Monograph and the Joint Breast Cancer Registry Annual Report 2022. The

Singapore Cancer Registry (SCR) is a national cancer registry established to collate information on population-based cancer trends in Singapore. The SCR's monograph included anonymised data on tumours diagnosed among Singaporean residents from 1 January 1968 to 31 December 2017. Data was obtained from notifications from medical practitioners, pathology and haematology laboratories and healthcare institutions. The 2020 Annual Report by the Joint Breast Cancer Registry (JBCR) is a prospective database of breast cancer patients managed in various SingHealth institutions such as Changi General Hospital, KK Women's and Children's Hospital, National Cancer Centre Singapore, Singapore General Hospital, and Sengkang General Hospital. This report included 28,628 patients older than 21 years, diagnosed from January 1960 to December 2019 and had a median follow-up of 5 years. Of the 28,628 patients, 25,529 were invasive breast cancer patients and 3,062 were non-invasive breast cancer patients. Data were retrieved from tumour boards, clinical databases and manual data entry. The JBCR is conducted with ethics approval by SingHealth Centralised Institutional Review Board. Both the SCR and JBCR databases are publicly available. In addition, TNBC patient data at Singapore General Hospital (SGH), comprising 289 patients diagnosed from 2007 to 2014 was analysed.

Study Variables

The independent variable chosen was ethnicity, a nominal variable, whereby patients were divided into 'Indian', 'Malay', and 'Chinese', which are the three main ethnic groups in Singapore. The analysis excluded data on those of other races from the registries. Furthermore, data extracted from both the registries (SCR and JBCR) included only patients with invasive breast cancer, excluding patients with carcinoma-in-situ.

The median age at diagnosis (years) and other variables on tumour characteristics such as subtype, staging and tumour grade were extracted from JBCR. Histological subtypes of breast cancer were defined as luminal A, luminal B, HER 2+ and TNBC, according to Goldhirsch et al. Patients were staged into Stages 1-4 as outlined in the AJCC 7th edition till January 2018, after which the AJCC 8th edition was followed. Survival was reported as Overall Survival (OS) and Disease-free Survival (DFS). Overall Survival (OS) was determined from the date of diagnosis of primary breast cancer to the date of death from any cause. Disease-free Survival was determined from the date of diagnosis to the date of any recurrence from primary breast cancer. Patients without the event, death or recurrence, during the survival analysis were censored on the date of the last follow-up. The Kaplan-Meier method was used for survival analysis.

Statistical Analysis

Statistical analysis was performed for the SGH data using SPSS software. The study outcome was presentation and prognosis; hence, the following dependent variables were considered: incidence, relative risk, median age at diagnosis, mortality, survival and tumour characteristics. The following variables were extracted from the SCR's monograph: incidence number, crude and age-standardised incidence rates, relative risk, mortality number, and crude and age-standardised mortality rate of breast cancer patients. The crude incidence or mortality rates, expressed as a rate per 100,000 population, were defined as the number of new cases or deaths divided by the at-risk population in a specific time period (SCR). Age-standardised rates, expressed as a rate per 100,000 population, were defined as the number of

new cases or deaths in a specific time period for a particular age group. Relative risks were reported with a 95% confidence interval (CI) and were calculated using the Chinese as a reference group.

Survival was reported as Overall Survival (OS) and Disease-free Survival (DFS). Overall Survival (OS) was determined from the date of diagnosis of primary breast cancer to the date of death from any cause. Disease-free Survival was determined from the date of diagnosis to the date of any recurrence from primary breast cancer. Patients without the event, death or recurrence, during the survival analysis were censored on the date of the last follow-up. The Kaplan-Meier method was used for survival analysis.

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, but at different rates. For the period of 2013-2017, the Chinese had the highest ASIR per 100,00 population (70.8), followed by the Indians (65.8) and the Malays (65.6), as in Table 1.

Additionally, as seen in Table 2, the median age at breast cancer diagnosis differs across the different ethnic groups. Malay patients are diagnosed at a 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 a lower percentage of cases detected clinically (77% and 76%, respectively).

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

	Chinese	Malay	Indian
Incidence			
Number	8668	1137	718
CIR (Crude Incidence Rate)	116.8	86.8	83.1
ASIR (Age-standardised Incidence Rate)	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	1638	339	157
CMR (Crude Mortality Rate)	22.1	25.9	18.2
ASMR (Age-standardised Mortality Rate)	12.0	19.1	14.5

Breast Cancer Survival and Mortality Rates

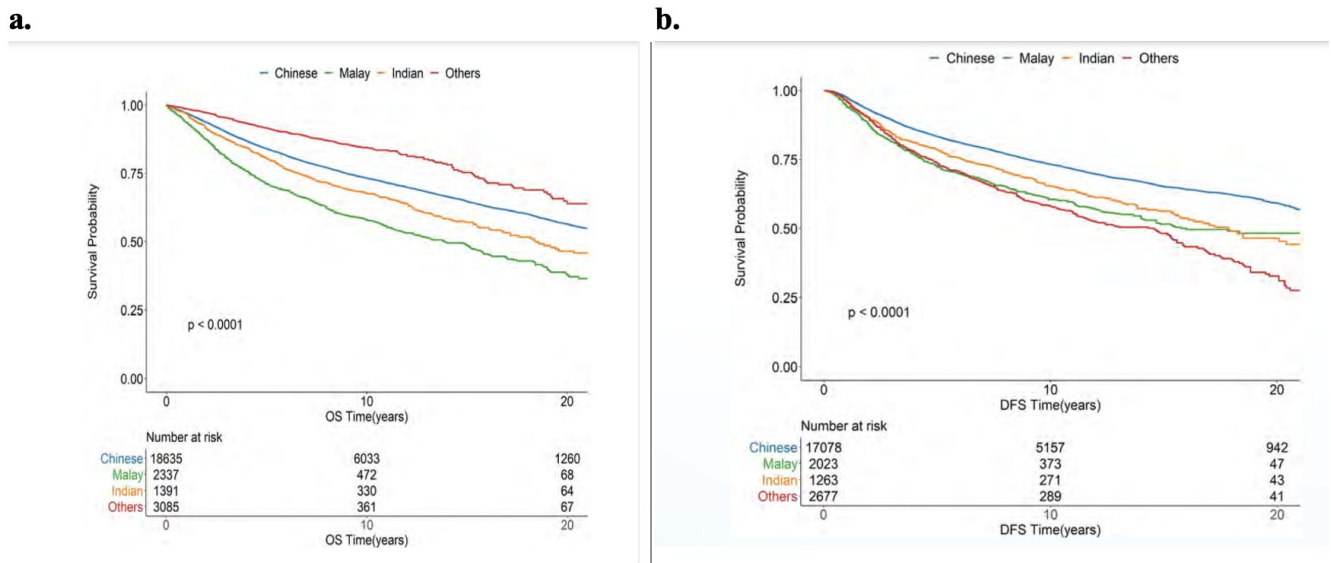


Figure 1. Overall survival (a) and disease-free survival (b) by ethnicity in breast cancer patients diagnosed from January 1960 to December 2019 (Joint Breast Cancer Registry, 2022).

Overall survival (OS) and disease-free survival (DFS) varied between the three ethnic groups. Malays had the poorest overall survival as compared to Chinese and Indians (Figure 1). In addition, at 10 years, Malays had the poorest disease-free survival, however, at 20 years, Indians had the poorest disease-free survival, lower than Malays. As seen in Table 1, although the ASIR was the lowest for Malays, the ASMR (Age Standardised Mortality Rate) for Malays has been consistently higher than 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).

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 (%) (n=9,206)			
Clinical	76	84	77
Radiological	24	16	23
Tumour Histological Subtype (%) (n=16,054)			
Luminal A	61	56	57
Luminal B	18	19	16
HER 2+ve	10	13	10
Basal	11	11	18
Tumour Grade (%) (n=20,852)			
Grade 1	15	9	12
Grade 2	41	35	42
Grade 3	44	56	46
TNM Staging (%) (n=26,050; DCIS/LCIS excluded)			
Stage 1	29	16	22
Stage 2	36	35	39
Stage 3	15	27	22
Stage 4	8	15	11
Type of Surgery (%) (n=18,889)			
BCS	27	28	30
Mastectomy	62	63	60
No surgery	11	9	10
Chemotherapy Given (%) (n=7,014)	66	76	64

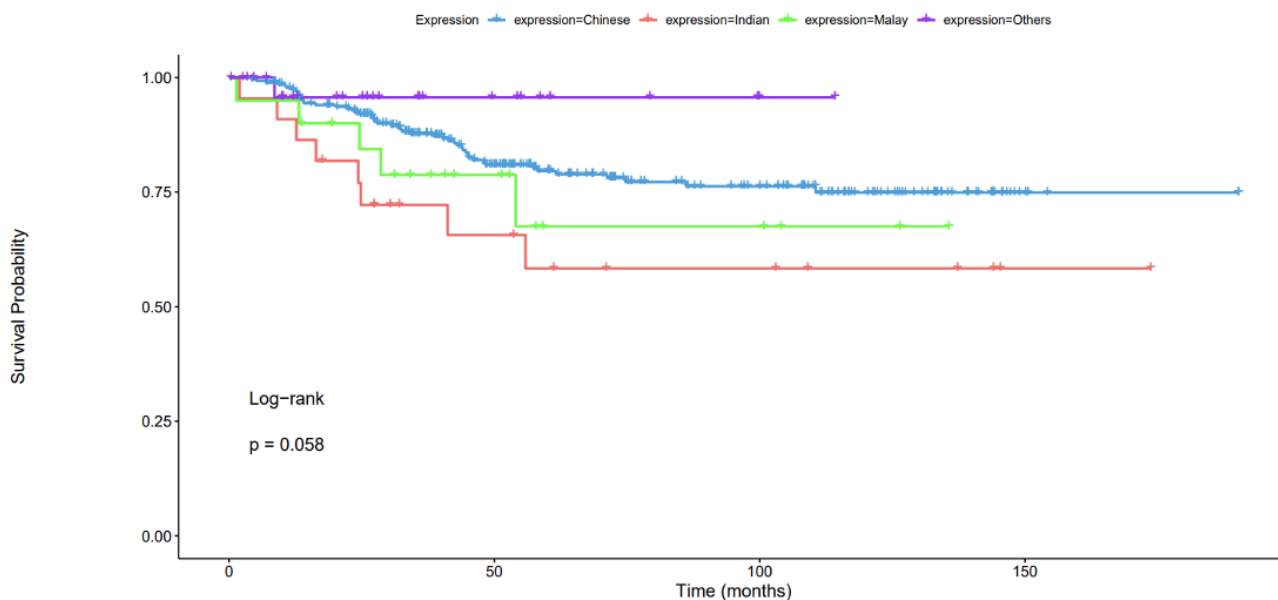
Breast Cancer Tumour Characteristics

In terms of histological subtype of breast cancer, Luminal A is the most common across all the ethnicities. It is present in 61% of Chinese, 56% of Malay, and 57% of Indians (Table 2). 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 the three major ethnic groups, Malays have a higher rate of Grade 3 tumours (56%) and the lowest rate of Grade 1 tumours (9%). Furthermore, Malays present with a higher percentage of advanced-stage tumours, stage 3 and stage 4 tumours. They have a higher percentage of stages 3 tumours (27%) as compared to Indians (22%) and Chinese (15%). In addition, they have a higher percentage of stage 4 tumours (15%), as compared to Indians (11%) and Chinese (8%).

Triple Negative Breast Cancer (TNBC)

Analysis of patients with TNBC cancer in our institution, SGH, indicated that Indians had a worse prognosis, where Indians had lower OS compared to Malays and the Chinese, as seen in Figure 2 below. Based on the same patient data, the correlation between ethnicity and DFS was not statistically significant.



b.

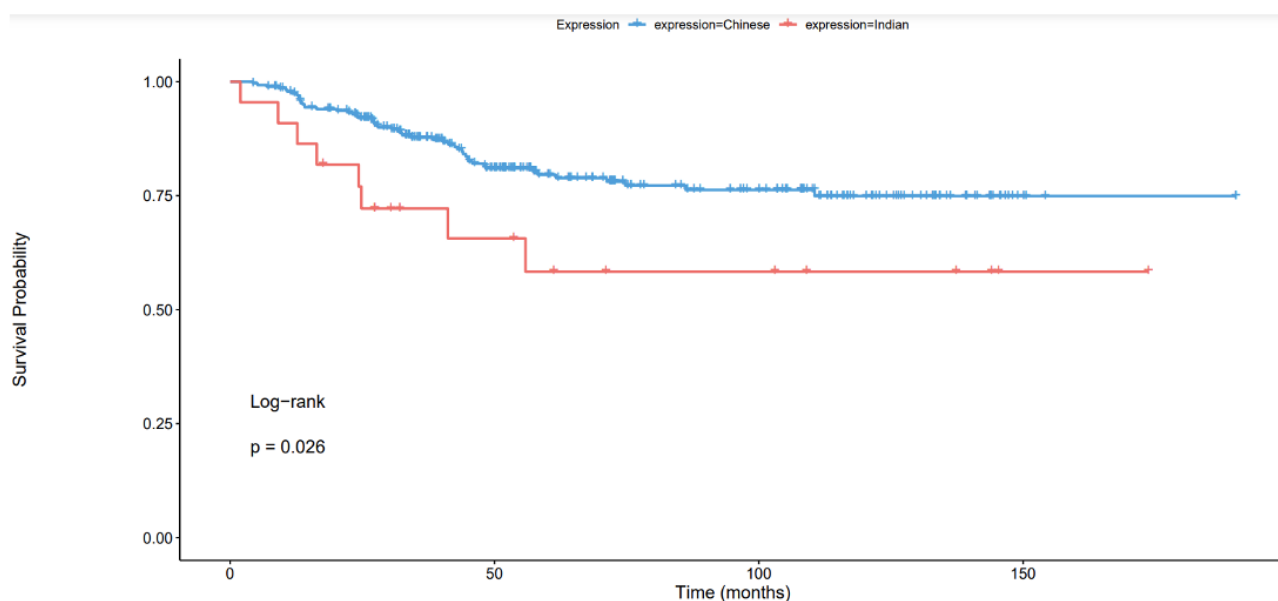


Figure 2. Overall Survival between (a) all three ethnicities and (b) Indians vs Chinese, as per in-house SGH TNBC patient data.

Discussion

This study suggests an association between ethnicity and presentation, tumour characteristics and prognosis in breast cancer patients in Singapore. Despite having a lower age-standardised incidence rate, it was found that Malay women have higher age-standardised mortality rates than the Chinese and Indians. At diagnosis, Malay women were more likely

to present at a younger age with advanced-stage and high-grade tumours. Lastly, overall survival was the lowest amongst Malays, whereas disease-free survival was the lowest for Indians at 20 years. Among TNBC patients, the prevalence was highest among Indian patients, who also had the poorest overall survival.

Our findings are consistent with previous research in Singapore and other Southeast Asian countries. A study in Malaysia found that Malays presented at a younger age and at a more advanced stage than the Chinese and Indians (Deniel et al., 2015). According to a local study based in Singapore and Malaysia, it was similarly found that Malays had the poorest 5-year overall survival and a significantly higher risk of mortality than other ethnicities (Bhoopathy et al., 2012). Furthermore, the same study found that Malay women were more likely to have axillary lymph node metastasis and distant metastasis.

Lower rates of radiologically detected tumours among Malay women indicate lower screening uptake in this group, despite equal access to health care in Singapore. This has also been reported in other studies in Singapore, where mammography uptake was found to be the 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). In addition, this study supports previous research that reported a higher prevalence of TNBC among Indians (Tang et al., 2019). While our study reports the poorest overall survival for Indians as compared to the Chinese, evidence of the association between ethnicity and survival in TNBC patients is conflicting in the literature. Another local study in Southeast Asia noted that ethnic variations did not impact OS and DFS in TNBC patients (Alcantara et al., 2017).

The association between ethnicity and breast cancer, as seen in our findings, is complex and may be explained by variations in several established breast cancer risk factors. Lifestyle factors such as dietary practices, obesity and breastfeeding rates undeniably play a role in risk and prognosis. Undoubtedly, different ethnicities have preferential choices for cooking styles or ingredients, and the effect of these varying dietary patterns on breast cancer has been well-studied in Malaysia, our neighbouring country with a similar ethnic distribution and climate. Indians and Malays have a greater tendency to use spices in their diet, such as curcumin which has been shown to have notable antitumour effects (Abdullah and Mohammad., 2021). It regulates cellular signalling pathways in cultured breast cancer cells by inhibiting the proliferation of breast cancer cell lines, T47D and MCF7, and decreasing the expression of CDC25 and CDC2 proteins while increasing the expression of P21 proteins (Hu et al., 2018). Higher consumption of fruit and vegetables was seen in the Malays, followed by the Chinese and Indians (Izzah et al., 2019), and has been associated with lower breast cancer risk (Heath et al., 2020). As such, diets involving curcumin, vegetables and fruits may explain the lower risks and incidence of breast cancer among the Malays and Indians compared to the Chinese, as seen in our study.

Obesity, more common in Malay and Indian women than in Chinese women, has been associated with late-stage presentation of breast cancer and substandard diagnostic workup (Bhoopathy et al., 2012). Furthermore, a meta-analysis reported that obesity was correlated with moderately worse DFS and OS in breast cancer (Lohmann et al., 2021). In obese patients, insulin resistance with hyperinsulinemia, altered adipokines levels with higher leptin and lower adiponectin, and increased oestradiol production may impact carcinogenesis (Lohmann et al., 2016). Obesity may also influence macrophage-tumour cell interactions and promote an immunosuppressive microenvironment (Singh et al.,

2022). Comorbidities associated with breast cancer may increase the risk of adverse breast cancer treatment effects (Schmitz et al., 2013). As such, Malays and Indians, for whom obesity and comorbidities are prevalent, are more often the groups with worse cancer survival outcomes.

Other factors that may influence breast cancer presentation and prognosis include socioeconomic status and cultural/religious beliefs. Barriers persist amongst Malay women in presentation and prognosis due to many factors, such as misinformation on breast cancer, perceived negative outcomes from mammography and worries about their treatment cost. Notably, all these factors are closely related to the socioeconomic 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 are 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). Additionally, in 2018, a focus group of 27 English-speaking Malay women in Singapore indicated religious beliefs such as Islamic values that prohibits revealing of the 'aurat' (intimate body parts) and spirituality to influence screening uptake (Shaw et al. 2018). Fatalism, a belief that some health issues are beyond human control, was found to be a barrier to screening and has been observed across ethnicities, but to a greater extent in Malays (Rajendram et al., 2022).

Lastly, variations in genetic factors may account for the ethnic differences in breast cancer presentation and prognosis. Germline genetics has been suggested to influence somatic gene expression and modulate tumour or immune microenvironment, which may explain the varying prevalence of breast cancer subtypes across ethnic groups (Yap, 2023). Chinese women have been found to have the highest incidence of *BRCA1* and *2* pathogenic variants at 63.1%, followed by Malay women at 23.1% and Indian women at 11.8%. (Thirthagiri et al., 2008). There was an equal proportion of *BRCA1* and *2* pathogenic variants among the Chinese women. There were more *BRCA2* pathogenic variant among the Malays. These mutations have been associated with an early onset breast cancer (age ≤ 40 years) (Abdullah and Mohamed., 2021). The higher proportion of *BRCA2* pathogenic variant may reflect selection bias, genetic drift, and a possible genetic or environmental factor modifying the penetrance of *BRCA1* or *BRCA2* among Malays (Thirthagiri et al., 2008). Moreover, differences in pharmacokinetics have previously been observed in Chinese, Malaysian and Indian women treated with doxorubicin (Ma, Hui, & Mok, 2010). It has been reported that SNPs in *SLC22A16* which are seen more frequently in Chinese women, are associated with an increased AUC of doxorubicin and doxorubicinol concentrations (Lal et al., 2017). Hence, certain treatments may therefore be more effective in one ethnic group than the other, particularly in Chinese women (BhooPathy et al., 2012).

Overall, the study has strengths and potential limitations. Strengths of this review include using nationally representative multi-institutional data from the registries on all breast cancer patients in Singapore and detailed information on breast cancer patients and tumour characteristics. However, as the registries do not provide information on TNBC patients, patient data at SGH was used to supplement the analysis. Hence, survival analysis of TNBC patients has limitations due to using single-centre data and a relatively smaller number of patients as compared to other studies. Moreover, some

patients were lost on follow-up, making it difficult to confirm an association between ethnicity and OS in TNBC patients. Further research must be carried out to thoroughly explore the association between ethnicity and TNBC prognosis in Singapore. Combining data on TNBC patients from multiple institutions will yield a larger sample size and may make it possible to make significant inferences. Furthermore, a more detailed analysis could be done to better understand the biological and cultural factors that lead to worse outcomes in Malays.

Conclusion

This study reveals distinct ethnic differences in breast cancer presentation and prognosis among TNBC patients in Singapore. Malay women have a higher likelihood of being diagnosed at a younger age and experiencing worse outcomes, including higher mortality rates and lower overall survival. They tend to have advanced-stage tumours and HER2 overexpression. Furthermore, breast cancer is more frequently detected clinically in Malay women, possibly due to lower screening rates. Among TNBC patients, Indians and Malays present earlier and have higher disease recurrence rates compared to Chinese. The reasons for these ethnic disparities are multifactorial, involving lifestyle factors, tumour biology, mutations, cultural/religious factors, and socioeconomic issues. Understanding these differences is crucial for targeted interventions and equitable clinical trial participation to improve breast cancer outcomes, especially for ethnic minorities.

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